The magnitude of Asthma-COPD Overlap (ACO) among patients diagnosed as Asthma and COPD.

A single center cross-sectional study.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE MD BRANCH XVII (TUBERCULOSIS AND RESPIRATORY MEDICINE) EXAMINATION OF THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI TO BE HELD IN

MAY 2018.

CERTIFICATE

This is to certify that the dissertation titled "The magnitude of Asthma-COPD Overlap (ACO) among patients diagnosed as Asthma and COPD" submitted towards fulfillment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University for the MD TUBERCULOSIS AND RESPIRATORY MEDICINE examination to be conducted in May 2018, is the bonafide work of Dr. Jefferson Daniel J, postgraduate student in the Department of Pulmonary Medicine, Christian Medical College, Vellore.

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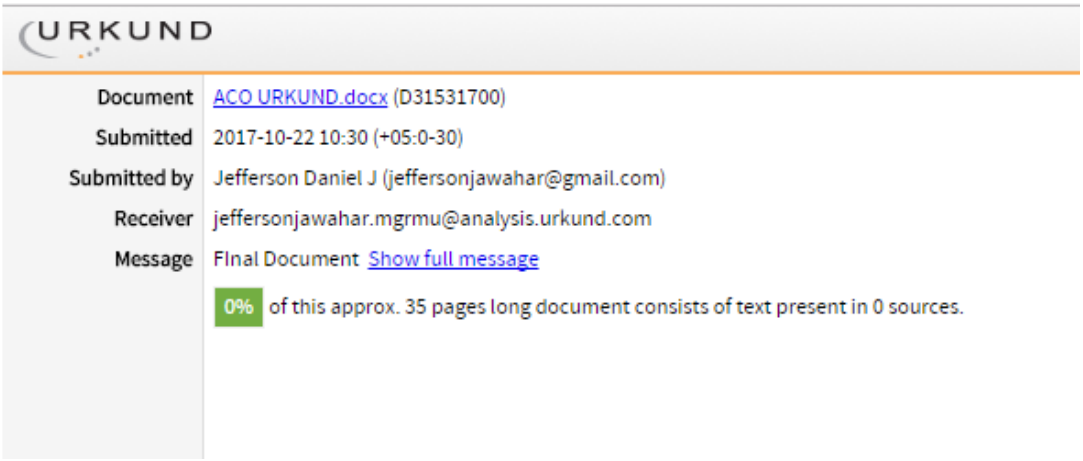
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"The young lions suffer want and hunger; but those who seek the LORD lack no good thing." – Psalm 34:10

I would like to thank The Lord Almighty to enable to me complete this project in a successful way. He chose me from the lowly places and have put me up where I'm today. Soli deo gloria!

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INTRODUCTION

Asthma, a chronic inflammatory state of the lung with cough and wheezing is often confused with Chronic Obstructive Pulmonary Disease (COPD) when present in individuals over the age of 40 (1). In contrast to Asthma, COPD although being a chronic inflammatory disease has a persistent airflow limitation (2). Differentiating the two had been a challenge in the past, but with significant research being done on this field, the Global Initiative for Asthma Management and Prevention (GINA) and its COPD counterpart, Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD) have laid down the principles by which the two can be differentiated (1,2).

The inflammation in asthma although usually eosinophilic, a neutrophilic phenotype is also recognized (3). Based on the composition of neutrophils and eosinophils, Asthma can be categorized into neutrophilic asthma, eosinophilic asthma, mixed granulocytic asthma and pauci granulocytic asthma (4). Whereas, COPD is predominantly a neutrophilic inflammation (5). The asthma phenotype with neutrophilic inflammation is more often associated with severe asthma and is poorly responsive to inhaled corticosteroids (6). People had varied opinion about these phenotypes, as some called this a separate entity with overlap of symptoms between asthma and COPD; while others prefer to call it as a phenotype of asthma itself.

These findings triggered an age old debate –'the Dutch hypothesis', which states that Asthma and COPD are different levels of the same disease spectrum as overlapping mechanisms may be present, in the gene – environment reaction that eventually results in the disease (7). The recent thinking on this subject is that there is at least an overlap of symptoms between asthma and COPD in certain patients, which has been termed as 'Asthma-COPD overlap Syndrome'. GINA have however renamed the term as Asthma-COPD overlap, ACO because it encompasses a cluster of patients with varying degrees of overlap. It is most often seen in patients who were asthmatic smokers. It was also not uncommon to find COPD patients with good post bronchodilator reversibility in lung volumes (8,9). This Asthma-COPD overlap is known by many names in many countries and a universal consensus has not yet been reached on this subject regarding its definite clinical pattern and diagnosis. However, the GINA and GOLD committees have together established a guidelines, by which a clinician can arrive at a diagnosis of Asthma-COPD overlap syndrome (ACO) (1,2)

Several published studies have concluded that ACO has worse prognosis than Asthma or COPD. Frequency of exacerbations, poor disease control, increased admissions, increased economic burden, and rapidly declining lung functions have been shown to be more in ACO in certain studies. Hence it is essential to diagnose and treat ACO at an early stage.

At the time when this study was initiated there were no reports available from India and the GINA syndromic approach to diagnose ACO had not yet been used in

any published study. The purpose of the study is to assess the magnitude of ACO in a tertiary care patient group in an Indian hospital using the GINA tool.

AIM OF THE STUDY:

Assessment of patients hitherto diagnosed to have Asthma or COPD fulfilling current criteria for ACO.

OBJECTIVES:

- To determine the prevalence of ACO in patients diagnosed as asthma, attending the pulmonary medicine OPD.
- To determine the prevalence of ACO in patients diagnosed as COPD, attending the pulmonary medicine OPD.
- To describe the clinical, radiological, spirometry characteristics of Asthma-COPD overlap.
- To compare the features of ACO with Asthma and COPD subjects in the study.

REVIEW OF LITERATURE:

History:

"Asthma" in Greek meant ‘to pant’, as first called by Hippocrates for a breathing disorder that correlated with changing climate and residence (10). Throughout human history across various civilizations, ancient writings have documented descriptions of illnesses that match with present day Bronchial Asthma. Alexander the Great was known to have used stramonium smoke, to relieve his breathing discomfort - stramonium was later identified to have anticholinergic properties (11).

Before 1600's there was no concept of COPD; and Asthma was known by many names with different treatments.

1679, Dr. Bonet termed ‘voluminous lungs’ to describe emphysematous lungs, (12)

1814, Dr. Charles Badham described bronchiolitis and chronic bronchitis. He claimed ‘catarrh,’ chronic inflammation of the mucosa is the basic pathology in bronchitis (13)

1821, Dr. René Laënnec, nailed emphysema to COPD. In his days smoking was not widely prevalent. Hence environmental and genetic factors were thought to cause emphysema or COPD.

1846, Dr .John Hutchinson and later Dr. Robert Tiffeneau, provided us with spirometry as a diagnostic tool to diagnose Asthma and COPD.

1900's the medical community started noticing that some wheezers had variable obstruction whereas others had more fixed obstructions.

1959, Ciba Guest Symposium defined the criteria that paved way for modern day COPD, which was then known as “chronic airflow obstruction” (14)

1961, Dr. Orie and colleagues: various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, are expressions of one common disease origin ‘chronic nonspecific lung disease’ (15).

1965, Dr. William Briscoe coined the term COPD (16).

1969, Dr. Fletcher and Pride names Orie's theory as ‘Dutch hypothesis’ (17).

1976, Dr. Charles Fletcher, made the association between smoking and COPD (18).

Today we know that Asthma and COPD are two different entities which was not known before the 17th century. With the number of smokers in the rise and with the life expectancy of Asthmatics increasing we are poised with a new problem. In our clinical practice, we face a lot of patients who seem to have both Asthma and COPD features. Can an Asthmatic smoker develop COPD? How will this mixed disease behave? Even as we refine our diagnostic skills in picking up obstructive airway disease early, we are faced with this daunting task of defining the overlap syndrome.

Epidemiology:

The International Study of Asthma and Allergies in Childhood (ISAAC) reports an incidence of 14% of asthma in Children worldwide (19). The total number of people living with Asthma in the world is roughly around 334 million according to the Global Burden of Disease Study (GBD) (19). WHO estimates that 235 million people currently suffer from asthma, 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD). More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally(20,21). In the Indian study on epidemiology of asthma, respiratory symptoms and chronic bronchitis in adults (INSEARCH), a survey conducted in two phases across 16 centers in India, the prevalence of asthma in adults was 2.05 per cent, with an estimated burden of 17.23 million (22).

There are very few studies that have looked into the incidence and prevalence of ACO, and so far, there are no Indian studies in this subject. After the study was initiated there were many publications on ACO based on a variety of criteria which are listed in the table.

S.NO	STUDY / AUTHORS	COUNTRY/ YEAR	FINDINGS
1	*Carlos a Vaz Fragoso, Terrence e Murphy et.al.*	USA 2017	N=3,486, 45.4% had asthma, 37.1% had COPD, 17.4% had ACO (23).
2	*Maria Montes de Oca, Maria Victorina Lopez Varela et.al.* **PUMA STUDY**	Latin America 2017	ACO in total population (by post BD FEV1/FVC<0.70 + asthma diagnosis) was 5.3 and 2.3% by post BD FEV1/FVC<0.70 + wheezing + reversibility. In previous asthma or COPD 17.9 and 9.9% by each definition as by the above criteria, and to 26.5 and 11.3% among COPD patients (24).
3	Hye Jung Park et.al.	Korea 2017	N: 1,504 COPD patients, 223 (14.8%) were diagnosed with ACO (25).
4	Inoue et.al.	Multicenter 2017	N: 1,008, 167 (16.6%) had ACO (26).
5	Jian Kang, Wanzhen Yao et.al.	China 2016	0.61% of Chinese population had ACO. 30.73% and 18.60% of

			asthmatics and COPD patients turned out to be ACO (27).
6	Jo YS, Lee J et.al	South Korea 2017	The incidence of ACO in study population was 31.3% by Spanish, 11.9% ATS Roundtable criteria, 48.3% PLATINO criteria, and 46.15% GINA criteria (28).
7	Milanese et al.	Italy 2014	29% in Asthmatics aged 65+ (29).
8	Golpe et al.	Spain 2014	5% in Tobacco induced COPD and 21.3% in biomass induced COPD (30).
9	Miravitlles et al	Multi center 2014	6.5% in COPD patients (31).
10	Fu et al	Australia 2014	56% in all obstructive airway disease patients of age >55 (32).

Diagnosis

Since the conception of the idea of an overlap between asthma and COPD, various criteria have been proposed by pulmonologists from different countries. The following table summarizes various criteria that have been proposed so far.

S.NO	STUDY / AUTHORS	COUNTRY/ YEAR	DIAGNOSTIC CRITERIA
1	Marsh et al,	New Zealand 2008	COPD (FEV1/FVC < 0.70) + Any of the following 1) post-BD increase in FEV1 ≥ 15%, 2) peak flow variability > 20% during 1 week of testing, and 3) Clinical diagnosis of Asthma with current symptoms or inhaler within one year (33).
2	Kauppi et al	Finland 2011	COPD (FEV1/FVC < 0.70 or FEV1/FVC < 88% predicted) + Any of the following 1) A post-BD increase in FEV1 of ≥12%, 2) A bronchodilator response of ≥15% or diurnal variation of ≥20% in PEF, and

			3) A decrease in FEV1 of ≥15% in the exercise test (34).
3	Kitaguchi et al	Japan 2012	COPD stage 2–4 (FEV1/FVC < 0.70 and FEV1 < 80%) + symptoms suggesting asthma such as episodic breathlessness, wheezing, cough, chest tightness with diurnal variation: more at night (35).
4	Juan Jose et al. SPANISH COPD GUIDELINES	Spain 2012	2 major criteria or 1 major and 2 minor criteria Major criteria: 1. Positive BDR≥400ml and 15% compared to baseline, 2. Eosinophilia in sputum and 3. History of asthma (prior to 40 years of age) Minor criteria: 1. Elevated total IgE, 2. History of atopy, 3. Positive BDR ≥200ml and 12% on at least two occasions (36).

5	Golpe et al.	Spain 2014	2 major criteria or 1 major plus 2 minor criteria. Major criteria: 1) Post-BD FEV1 increase ≥15% and ≥400 mL over baseline, 2) FENO > 40 ppb, and 3) Personal history of asthma. Minor criteria: 1) Elevated serum IgE, 2) History of atopy, and 3) Post-BD FEV1 increase ≥12% and ≥200 mL over baseline on 2 or more occasions (30).
6	Cosio BG et. Al. CHAIN STUDY	Spain 2016	1. Bronchodilator test (BDR)>400ml and 15% or a history of asthma 2. Eosinophilia >5%, 3. IgE> 100IU/ml or two BDR>200ml and 12 % (37).
s7	Sin et al.	Consensus among specialists in North	Major criteria: 1. Persistent airflow limitation 400ml in FEV1 Minor criteria:

		America, Europe and Asia 2016	1. Documented history of atopy or allergic rhinitis, 2. BDR≥200ml and 12% on at least 2 occasions, 3. Peripheral eosinophilia≥300 eosinophils/µL). Major criteria and at least one of the minor criteria proposed had to be met (38).
8	Miravitlles et al.	New consensus between GesEPOC and GEMA	1. Presence of chronic persistent airflow limitation, in a smoker or former smoker [tobacco exposure≥10 pack-years] with 2. Concomitant diagnosis of asthma or with characteristics of asthma such as very positive BDR (≥15% and ≥400ml) and/or blood eosinophilia (≥300 eosinophils/µL) (39).

However, the most extensively used guidelines is the GINA-GOLD syndromic approach table as below. More than three features for a particular disease favors that diagnosis; an equal number of features for both diseases is most likely to be ACO (1).

	ASTHMA	**COPD**
Age of onset	Before 20	After 40
Pattern of symptoms	1. Variation over minutes, hours or days. 2. Worse during the night or early morning. 3. Triggered by exercise, emotions including laughter, dust or exposure to allergens.	1. Persistent despite treatment. 2. Good and bad days but always daily symptoms and exertional dyspnea 3. Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers.
Lung function	Record of variable airflow limitation.	Record of persistent airflow limitation.
Lung function between symptoms	Normal	Abnormal
Past history / Family History	1. Previous doctor diagnosis of asthma. 2. Family history of asthma and other allergic conditions.	1. Previous Doctor diagnosis of COPD - Chronic bronchitis or emphysema. 2. Heavy exposure to risk factor: tobacco smoke, bio mass fuel.
Time Course	1. No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year. 2. May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks.	1. Symptoms slowly worsening over time (progressive course over the years). 2. Rapid - acting bronchodilator treatment provides only limited relief.
Chest X ray	Normal	Sever Hyperinflation

Various studies used different criteria and noticed the difference in prevalence percentage as highlighted by Jo YS, Lee J et.al. The incidence of ACO in the study population varied based on the criteria that was used: 31.3% by Spanish, 11.9% by ATS Roundtable criteria, 48.3% by PLATINO criteria, and 46.15% by GINA criteria (28).

A patient with evidence based diagnosis of bronchial asthma due to various factors can progress over many years and develop a permanent fixed airway obstruction. This is a phenotype of asthma known as 'asthma with fixed airway obstruction' rather than ACO. When an Asthmatic who smokes develop non-fully reversible airflow obstruction, he may go on to develop features of both asthma and COPD. This is more likely to be ACO. A patient with evidence based diagnosis of COPD have a genetic Th2 background, they can have high eosinophil counts in peripheral blood. This could be ACO. But when a COPD patient has good reversibility, it does not mean that it could be asthma or ACO unless there are other compelling evidence as quoted in the diagnostic criteria section. But if the reversibility is more than 400 mL and 12% then ACO could be considered, provided Asthma is ruled out (24,27).

There are not many studies that have validated GINA syndromic method of diagnosis. Hence a study on this field with these criteria would be needed to evaluate its effectiveness. It will also provide an insight into the ACO in an Indian context.

Spirometry:

Spirometry is a vital test to aid in the diagnosis of Asthma-COPD overlap. The following table represents the vital differences in spirometry between Asthma, COPD and ACO.

VARIABLE	**ASTHMA**	**COPD**	**ACO**
FEV1/FVC Normal	Can be present	Cannot be present	Cannot be present unless other evidence of chronic airflow limitation
Post BD FEV1/FVC <0.7	Can be present	Should be present	Usually is present
Post BD FEV1>= 80% pred	Usually present in well controlled.	GOLD mild obstruction	Can be present
Post BD FEV1 < 80% pred	Can be present	Usually is present	Usually is present
Post BD increase in FEV1 >=12% & 200 mL	At some point before treatment usually	Can be present when there is low FEV1	Can be present when there is low FEV1
Post BD increase in FEV1 >=12% & 400 mL	High probability of asthma	Unusual	Can be present

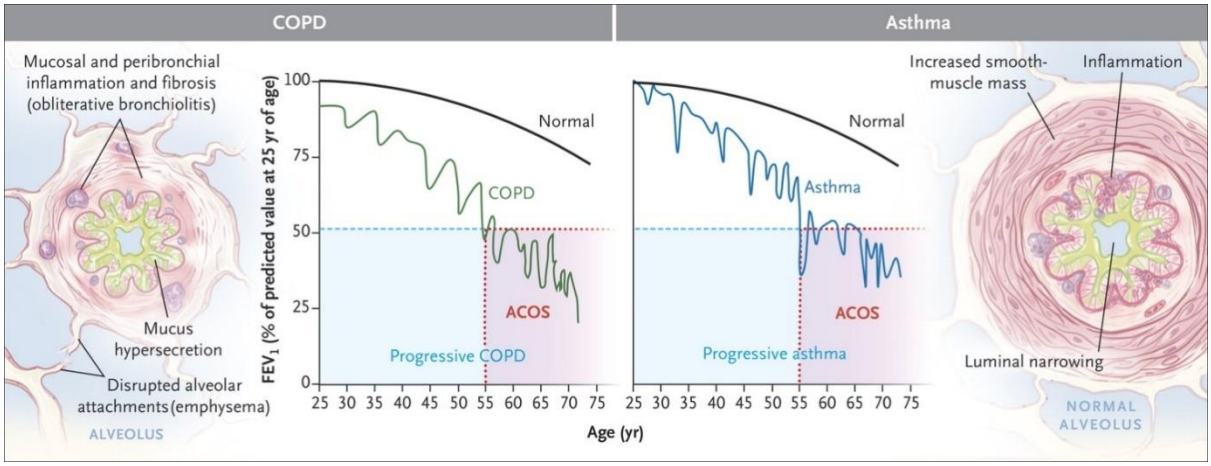


Figure 1 Rate of decline of FEV1 in Asthma vs COPD

The above image depicts the nature of the rate of decline of FEV1 over the years for both COPD and Asthma; and how beyond certain degree of severity, the lung function in both the diseases resemble ACO. COPD in general has a rapid decline in FEV1(40).

Pathogenesis

It is well known that the underlying pathology in asthma and COPD are different. ACO have inherited several pathological characteristics from both Asthma and COPD just like how it shares common clinical features.

Asthma is predominantly an eosinophilic inflammation, caused by release of pro inflammatory cytokines and proteins, that can cause damage to the airway epithelial cells. Airway remodeling is an eventual consequence of such chronic injury and inflammation (41). Mast cell activation activates innate and adaptive immunity on exposure to infection and normally to tissue injury. They are also involved in processes that involve inflammation and remodeling of tissue structure. In such cases mast cells are often inappropriately and chronically activated. Recent research have shed light on how mast cells have been involved in the pathogenesis of both Asthma and COPD (42,43). Apart from mast cells macrophages, lymphocytes and dendritic cells also are involved in maintaining airway inflammation (44).

Although eosinophilic asthma is the predominant type, a non-eosinophilic, neutrophilic type of asthma is also prevalent (45,46). Such a neutrophilic asthma is usually seen in severe or late onset asthma and in airways of smokers (47). In this special subset of patients, the bronchial infiltrate is rich in CD8(+) T cells and CD68(+) macrophages. Particularly in smoking asthmatics, due to constant injury to the epithelium caused by the noxious stimuli, remodeling sets in, which is similar to COPD (48).

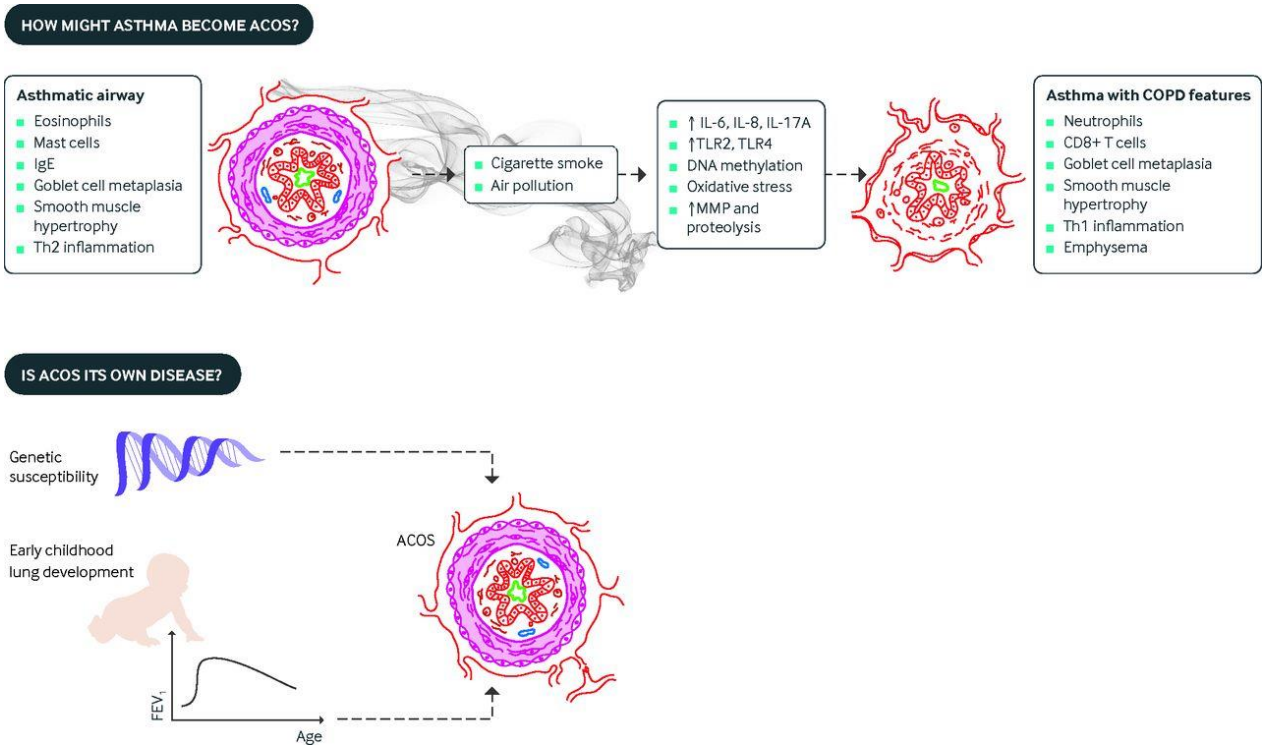


Figure 2 Two mechanisms by which ACO may develop.

There are two hypotheses for development of ACO- First is the Dutch hypothesis, where Asthma and COPD are two ends of a same spectrum of which ACO is in the centre. If an asthmatic is exposed to COPD risk factors his disease behaves like ACO. Second is the British hypothesis, all Asthma, COPD and ACO are unique diseases with separate pathogenesis (49).

Whereas the inflammation in COPD is marked by an increase in CD8+ (cytotoxic) Tc1 lymphocytes, macrophages and dendritic cells seen particularly in smokers (50,51). There are other reports which suggest the presence of an eosinophilic inflammation in severe COPD exacerbations as well (52). The ECLPSE cohort study

also highlights the presence of an elevated eosinophilic counts in a subset of COPD patients (53).

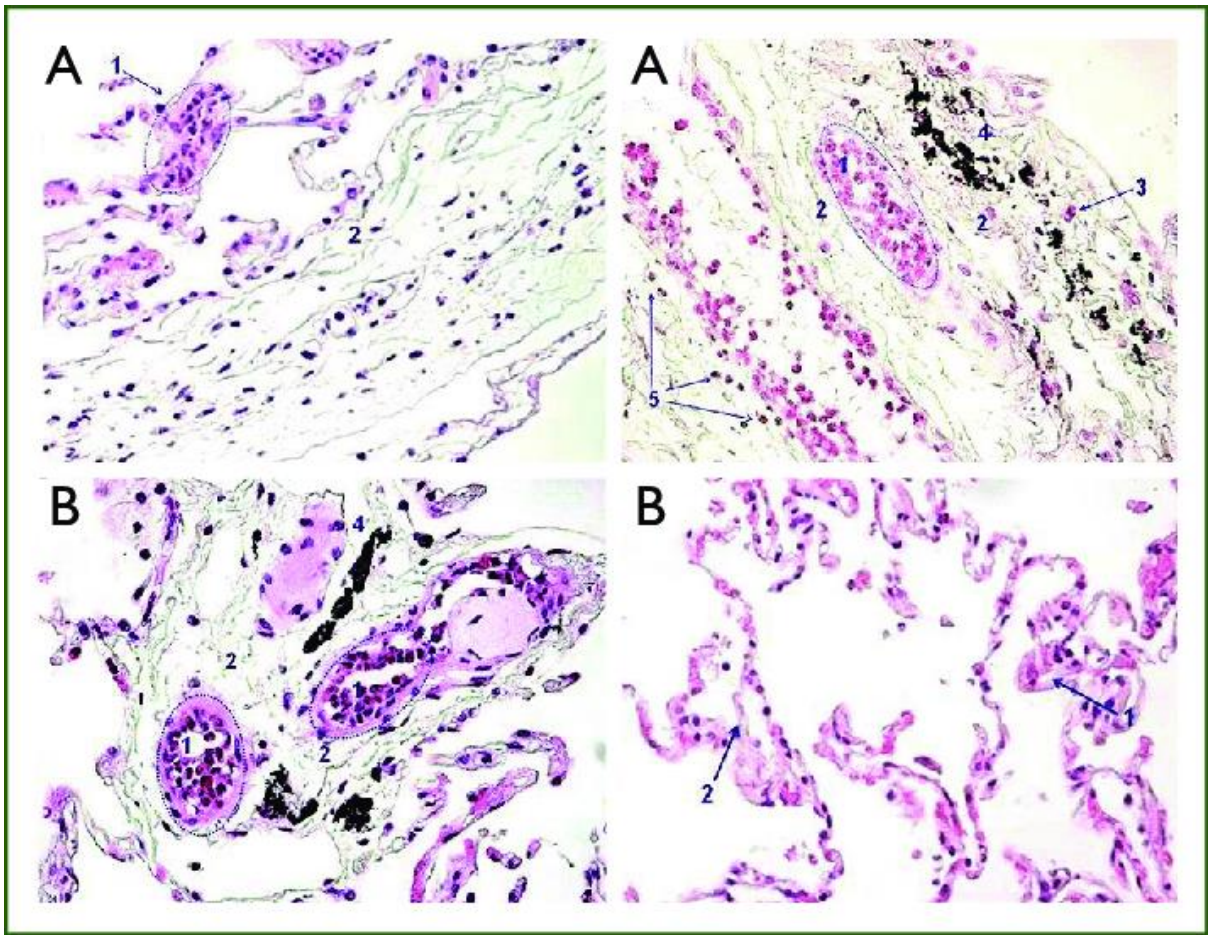


Figure 3 ACO lung histopathology

1) Eosinophils polymorphonuclear leukocytes;
2) Meso alveolar septum;
3) Hyperemia of small blood vessels;
4) Deposition of carbon granules;
5) Leukocytes outside vessel luminal.

In patients with eosinophilic inflammation, differences in CD83(+) dendritic and B cells make them steroid insensitive (54). This could be attributed to smoking. Moreover, perforin and 8-OHdG also get activated in smokers who have eosinophilic inflammation, which is otherwise seen only in COPD (55,56).

In certain ACO patients, mitochondrial dysfunction, which is one of the many mechanisms in the development of COPD have been identified. Also, genetic mutations like SNPs in the genes CSMD1 and GPR65 have also been discovered (57). ACO patients have higher diffusing capacity, greater airway wall thickness and higher pulmonary microvascular density than COPD patients (58).

Management

ACO management has to be personalized from patient to patient. Patients can develop ACO from both an Asthma background or a COPD background. There are very few studies about the response of ACO to treatment with different drugs, mainly because ACO patients are excluded from most studies that concern Asthma or COPD. The following are the list of drugs that could be used to manage ACO.

General Measures:

1. Smoking cessation,
2. Oxygen supplementation,
3. Pulmonary rehabilitation,
4. Vaccines and
5. Management of comorbidities (59).

LIST OF DRUGS THAT ARE USED IN THE MANAGEMENT OF ACO		
DRUGS	STATEMENT	REFERENCE
ICS LABA COMBO	Most studies recommend this as the first line of treatment for ACO.	(60,61)
SABA prn	Cannot be given alone but can be used as a rescue.	(1,2)
ICS only	Usually not recommended.	

Leukotriene receptor antagonists	Can be useful in ACO as studies have shown response in Asthmatic smokers.	(62)
Mast Cell Stabilizers	Mast cells have been extensively established in the pathogenesis of smoking in eosinophilic inflammation and COPD. Hence Mast Cell stabilizers have shown to be useful in ACO.	(63,64)
Theophylline	It modulates corticosteroid activity and augments ICS activity.	(65)
LAMA	Have shown benefit both in severe asthma and in COPD. Is recommended to be used with LABA ICS combination.	(66)
PDE inhibitor	Positive beneficial effect along with ICS/LABA/LAMA	(67–69)

For all practical purposes when ACO is suspected it is best to start an ICS LABA combination first. Then depending on the predominant nature of the disease, whether it behaves like an asthma or COPD, either theophyllines or Montelukast can be added.

MATERIALS AND METHODS:

Study Type:

This is an Cross-sectional study done in Christian Medical College, Vellore, Tamil Nadu

Study Design:

This study was designed to be a cross sectional study. Patients who were visiting pulmonary medicine outpatient department on a regular basis for management of Bronchial Asthma or COPD were observed and analyzed, if they had characteristic features suggestive of ACO, as defined by GINA guidelines. The patients were enrolled in the study if they fulfilled the inclusion criteria. Only patients who review in the hospital for at least 6 months were included in the study.

The study patients were randomly selected from the computerized OPD appointment list. After informed consent, the study proforma was administered. Their Spirometry, 6-minute walk test, IgE, % of peripheral eosinophils were documented.

GINA syndromic approach table was used to re visit diagnosis in these patients. The data was then documented using Epidata software and analysis was done using SPSS software.

Duration of the study:

The study was conducted between November 2016 and January 2017 (3 months).

Sample size:

This is a cross sectional study. When the study was designed there was no data about the prevalence of ACO based on GINA criteria anywhere in the world. There were no published data in India based on any of the known ACO criteria. Hence 60% each of Asthma and COPD were included in the study.

Inclusion Criteria:

All patients attending the pulmonary medicine OPD with a prior diagnosis of Asthma and COPD, were included.

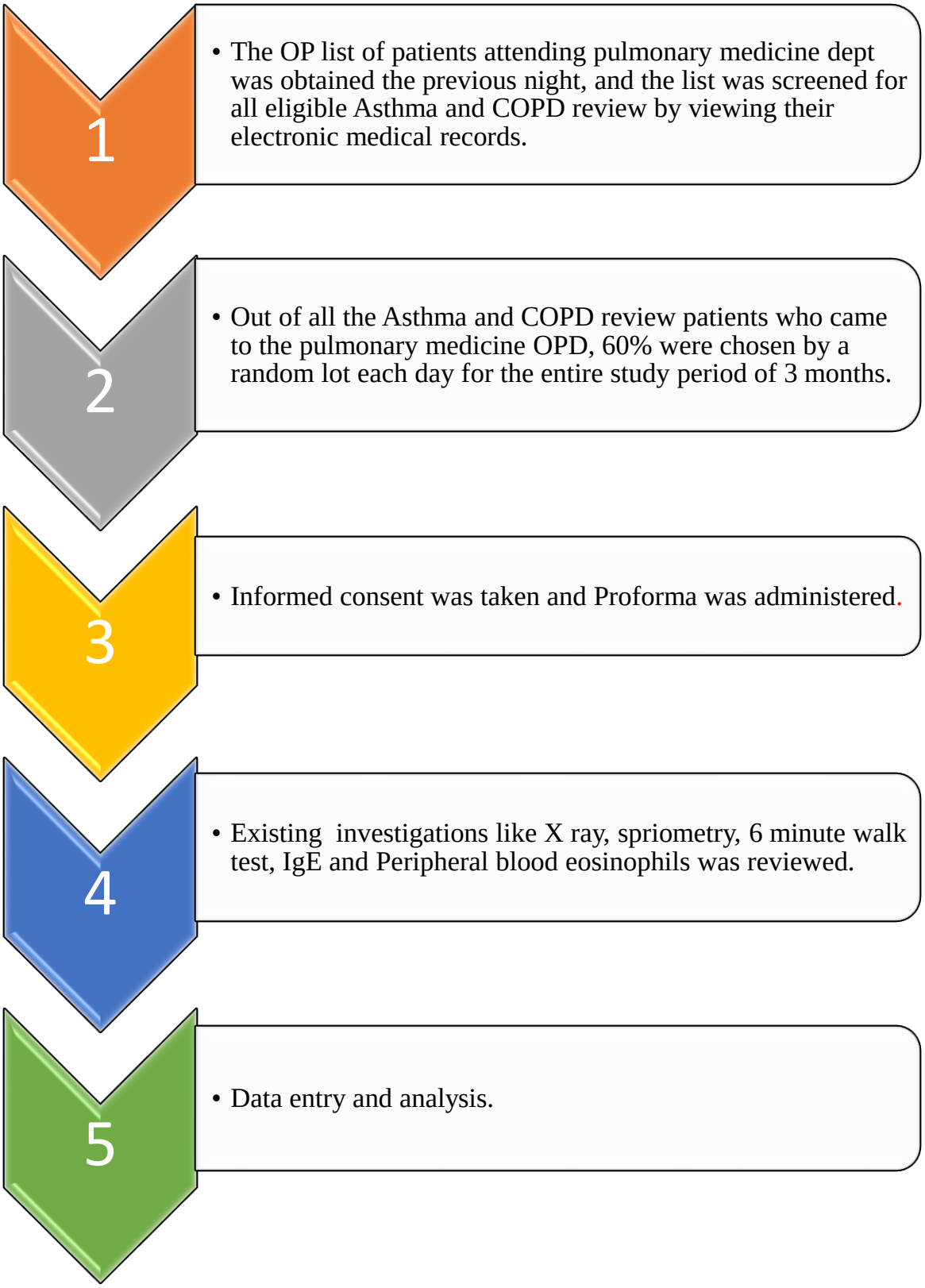
Exclusion Criteria:

1) Age less than 18.
2) Other pulmonary morbidities such as Bronchiectasis, Pulmonary TB sequelae, Lung malignancy, Interstitial Lung disease etc.
3) Patients who had been diagnosed within 6 months.

Patient recruitment

During the study period, 60% of all previously diagnosed Bronchial Asthma and COPD patients, on their review visit to the department of Pulmonary medicine OPD in Christian Medical College, Vellore were enrolled. All included patients were provided with the study details in the form of patient information sheet in the language they understood and was explained by the principal investigator after which a written informed consent was obtained. (Annexure).

Study Algorithm:



Statistical Analysis:

Data entry will be done in Epidata version 3.1 and analysis will be done using SPSS version 16.0

Descriptive statistics will be reported using mean +/-SD for continuous variables like (age, FVC, 6-minute walk distances etc.) which are normally distributed. Categorical variables such as sex, adverse events, will be reported using frequency and percentage association between the outcome.

Funding:

The institutional review board provided funding for this study.

Institutional review board approval and ethical considerations:

The study was presented to the Institutional review board and was approved by it and by the ethics committee of Christian Medical College, Vellore (IRB Min No: 9844 (OBSERVE) dated (7.01.2016).

RESULTS:

For further discussion and in order to avoid confusion, the original Asthma patients who were included in the study are here after known as **"Pre-Study Diagnosis of Asthma (PSDA)".** The original COPD patients who were included in the study are here after known as **"Pre-Study Diagnosis of COPD (PSDC)".** After application of the GINA-GOLD syndromic approach tool for ACO, a new set of Asthma, COPD and ACO are diagnosed. They will be known as **'Confirmed Asthma', 'Confirmed COPD' and 'Confirmed ACO'.**

Baseline characteristics of Pre-Study Diagnosis of Asthma (PSDA):

The baseline characteristics of the 713 Pre-study diagnosis of asthma patients who were enrolled into the study after fulfilling the inclusion and exclusion criteria are as follows:

Table 1: Baseline Characteristics of Pre-Study Diagnosis of Asthma (PSDA) patients.

PARAMETER	VALUE
1. Gender	Males: 296 (41.5%) Females: 417 (58.5%)
2. Age Group	18 to 40 years: 272 (38.1%) 41 to 60 years: 302 (42.4%) 61 to 80 years: 133 (18.6%)

	Above 80 years: 6 (0.9%)
3. Smoking history	32 (4.49%)
4. Biomass fuel exposure	175 (24.5%)
5. Family history of Asthma	211 (29.6%).
6. Allergic Rhinitis	606 (85.35%)
7. Spirometry	FEV1/FVC <0.7: 252 (35.3 %) FEV1/FVC >0.7: 461 (64.7%)
8. Significant reversibility	206 (29.6%)
9. Regular follow-up	664 (93.4%)
10. Hyperinflation in X ray	86 (12%)

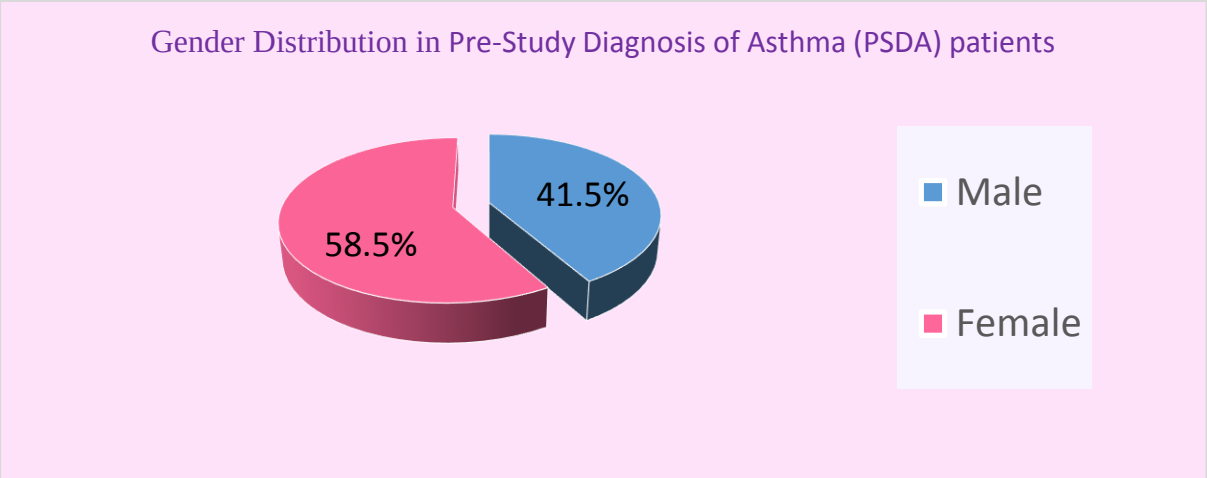


Figure 4 Gender breakup – PSDA. N = 713

Among the 713 asthma patients who were included in the study majority of them were women (417 women, 58.5%).

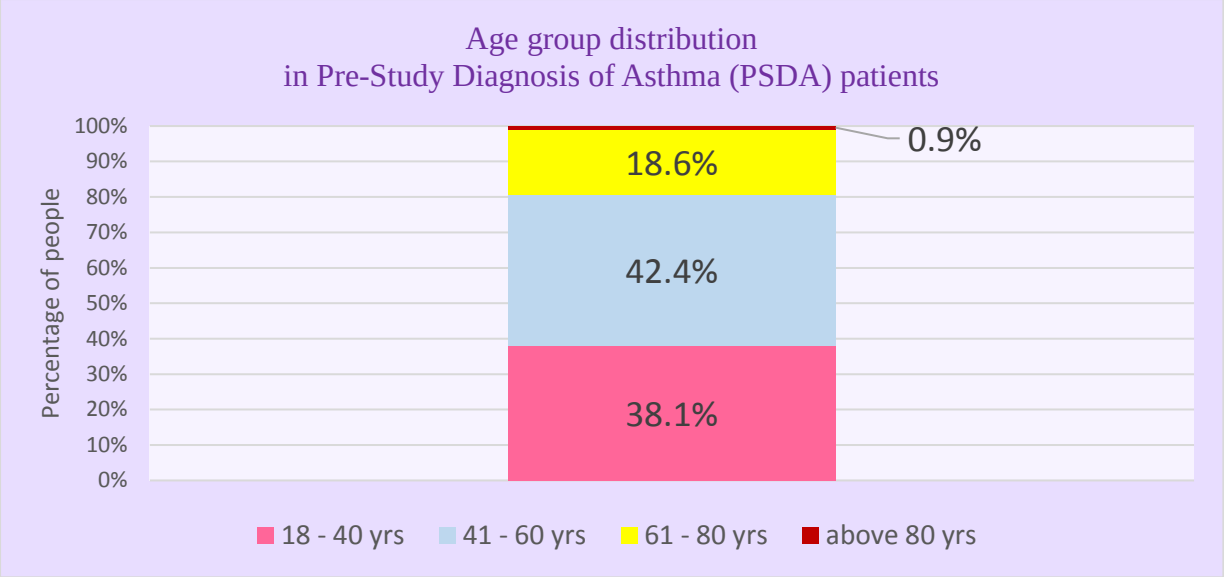


Figure 5 Age group breakup – PSDA. N = 713

Most of the pre-study asthma patients were less than 60 years of age (More than 80%). About 38.1% of them were less than 40 years of age.

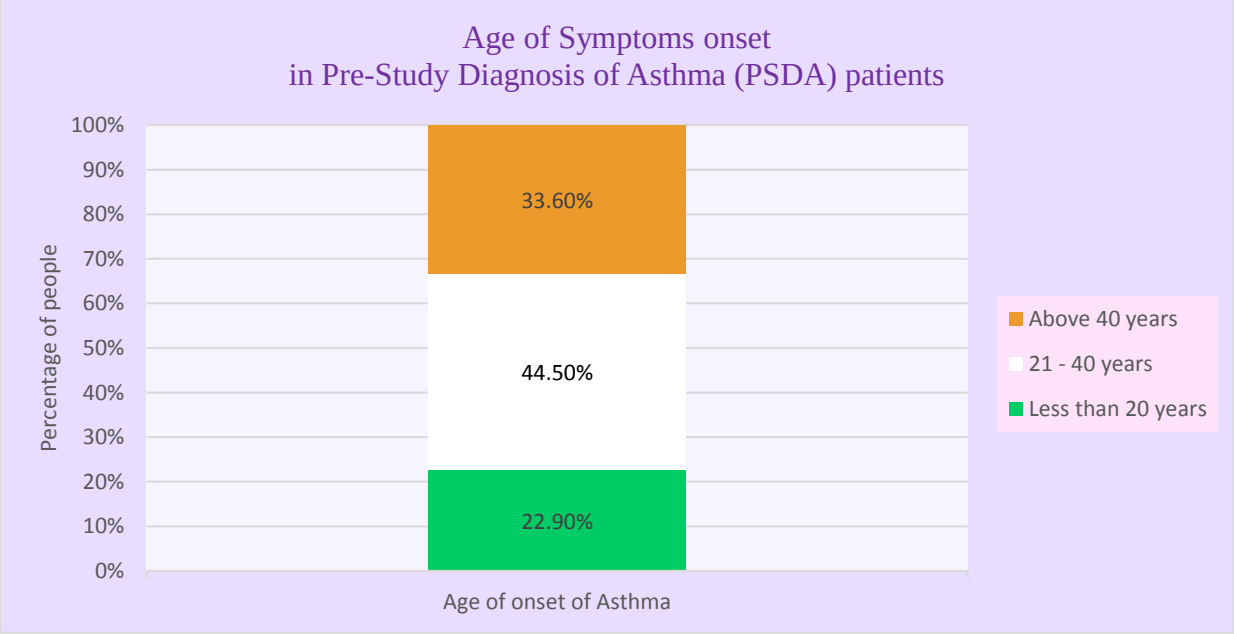


Figure 6 Age of Symptoms onset in Pre-Study Diagnosis of Asthma (PSDA) patients. N = 713

Two thrids of the pre-study Asthma group had onset of Asthma symptoms before 40 years of age.

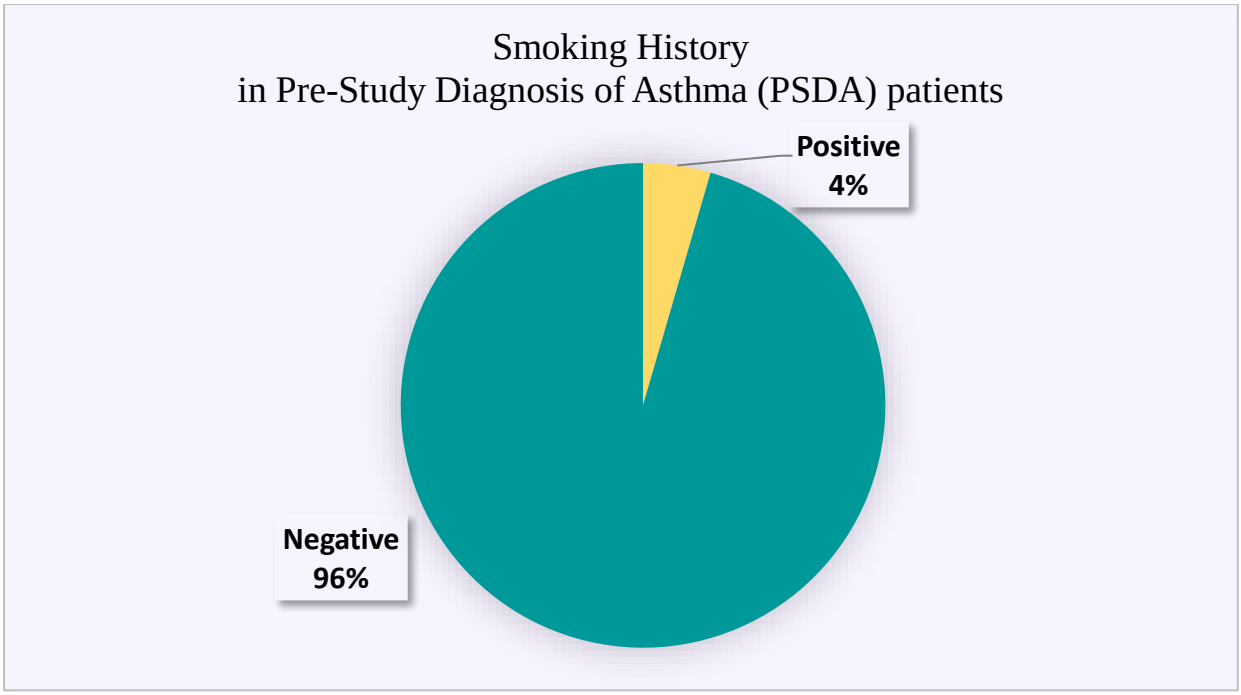


Figure 7 Smoking History in Pre-Study Diagnosis of Asthma (PSDA) patients. N = 713.

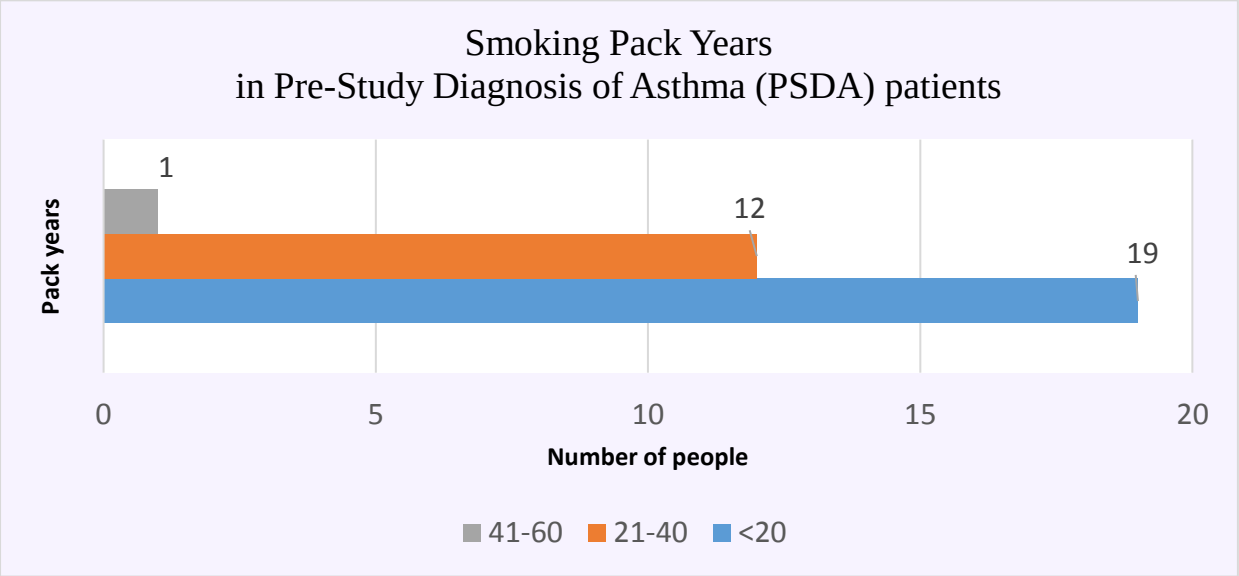


Figure 8 Smoking Pack Years in Pre-Study Diagnosis of Asthma (PSDA) patients. N = 32 (4% of 713)

Of the 4 % smokers in the Asthma group, majority of them had less than 20 pack years history. Around 40% of the pre- study asthma smokers had more than 20 pack year history.

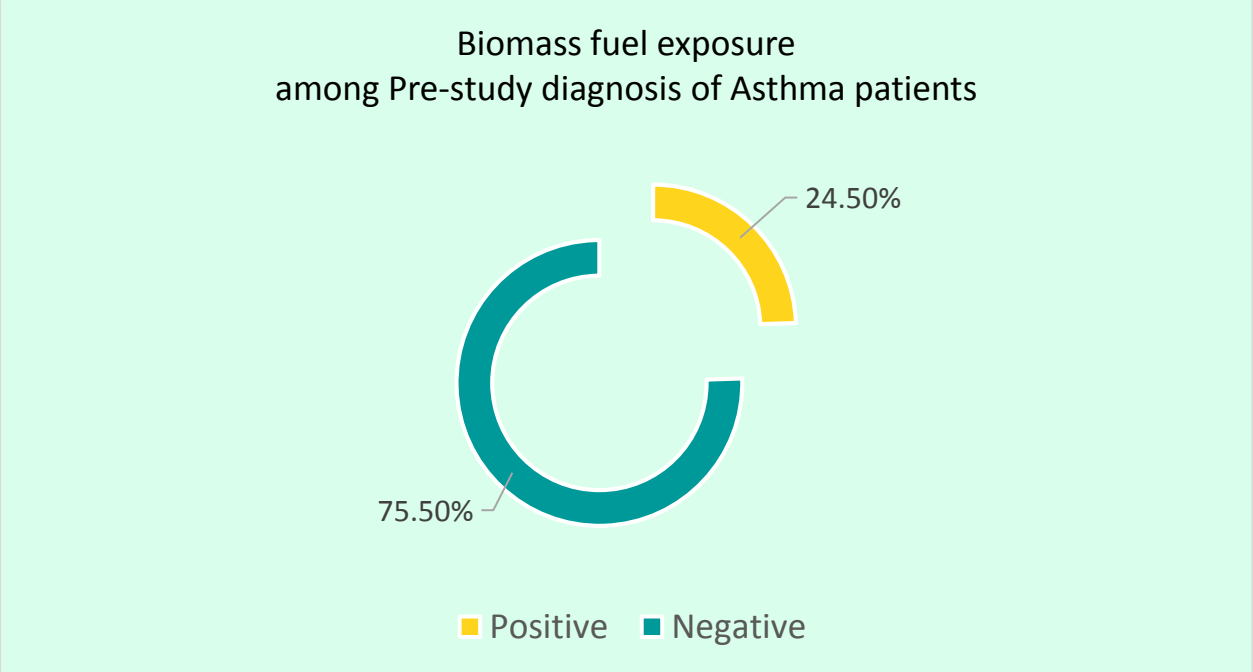


Figure 9 Biomass fuel exposure among PSDA Patients. N = 713

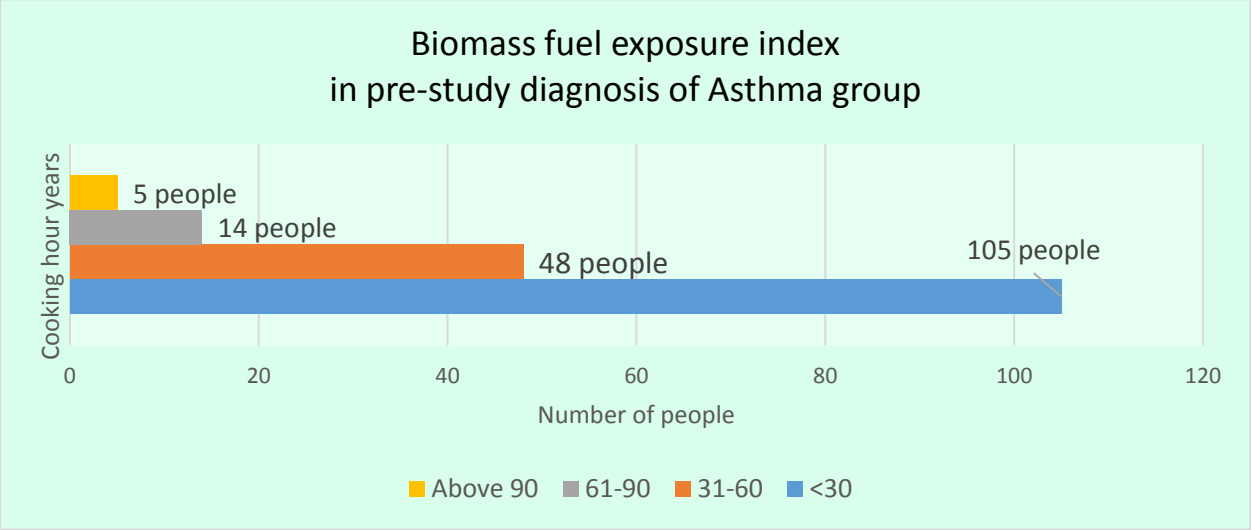


Figure 10 Biomass fuel exposure index in pre-study diagnosis of Asthma group. N = 172 (24.5% of 713)

Up to 25% of the PSDA Asthma patients had exposure to biomass fuels. A minimum threshold of biomass exposure index of 60 will lead to development of COPD especially in women (70). Among PSDA asthma patients only 2% had significant BMF index of more than 60.

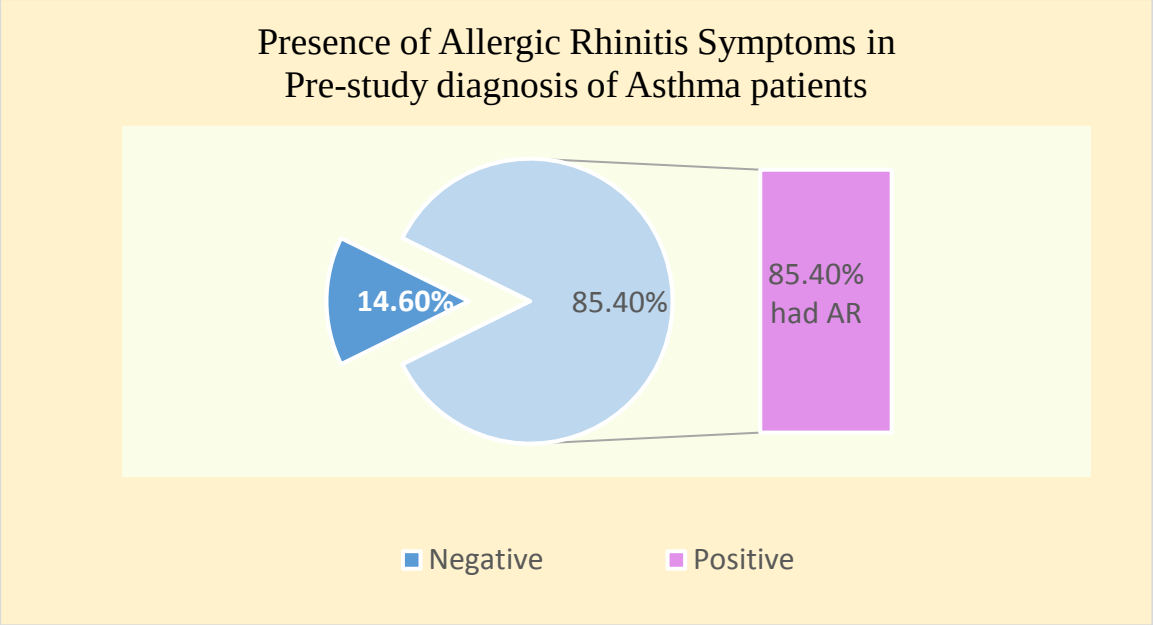


Figure 11 Presence of Allergic Rhinitis Symptoms in Pre-study diagnosis of Asthma patients. N = 713

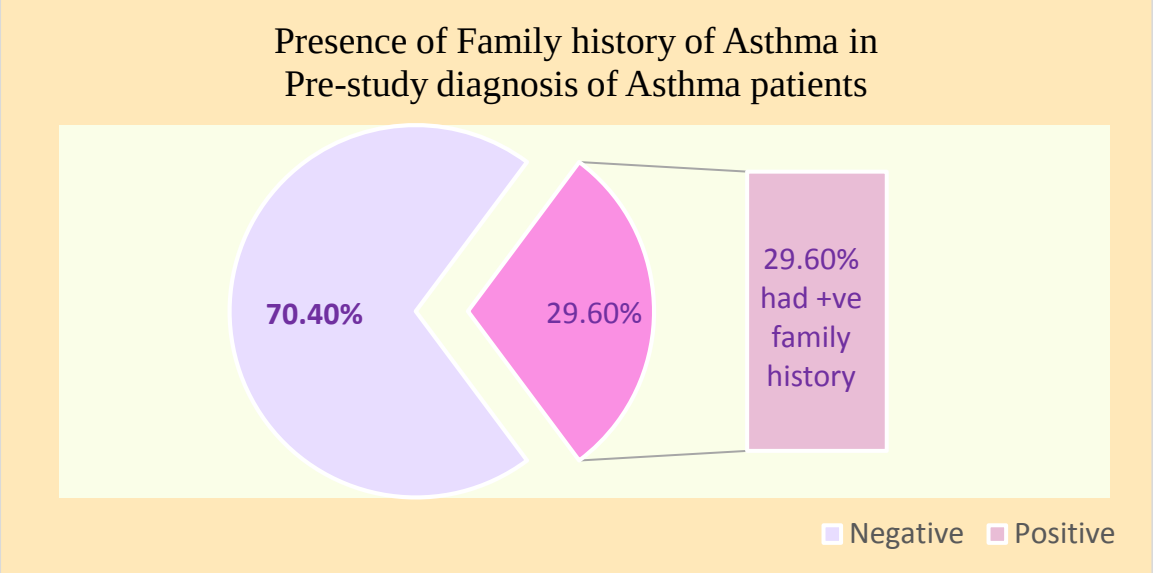


Figure 12 Presence of Family history of Asthma in Pre-study diagnosis of Asthma patients. N = 713

Allergic Asthma is a common phenotype. Allergic rhinitis and bronchial Asthma often coexist together. Among the known Asthmatics who participated in the study 85% of them had a history suggestive of Allergic Rhinitis.

In our study only 30% of the previously diagnosed Asthma patients had a positive family history for asthma.

Table 2: Treatment history in asthma

TREATMENT	TOTAL
SABA ONLY	0
ICS ONLY	47, (6.66%)
TIOTROPIUM ONLY	6, (0.85%)
ICS LABA	366, (50.92%)
MONTELUKAST ONLY	2, (0.28%)
ICS LABA MONTEL	196, (27.76%)
ICS MONTEL	3, (0.42%)
ICS LABA TIOTROPIUM	98, (13.88%)
TOTAL	713

Among the pre-study diagnosis of Asthma (PSDA) patients, 50% were on only ICS LABA combination, whereas 99% of the asthma patients received inhaled corticosteroids.

Baseline characteristics COPD

The baseline characteristics of the 157 Pre-study diagnosis of COPD (PSDC) patients who were enrolled into the study after fulfilling the inclusion and exclusion criteria are as follows:

Table 3: Baseline Characteristics of COPD patients.

PARAMETER	VALUE
1. Gender	Males: 134 (85.3%) Females: 23 (14.6%)
2. Age Group	18 to 40 years: 0 41 to 60 years: 41 (26.1%) 61 to 80 years: 112 (71.34%) Above 80 years: 4 (2.5%)
3. Smoking	122 (77.71%)
4. Biomass fuel exposure	20 (12.74%)
5. Family history of Asthma	12 (7.6%)
6. Allergic Rhinitis	33 (21%)
7. Spirometry	FEV1/FVC <0.7: 119 (75.8 %) FEV1/FVC >0.7: 38 (24.2%)
8. Significant reversibility	24 (22.82%)
9. Regular follow-up	142 (90.5%)
10. Hyperinflation in X ray	109 (69.4%)

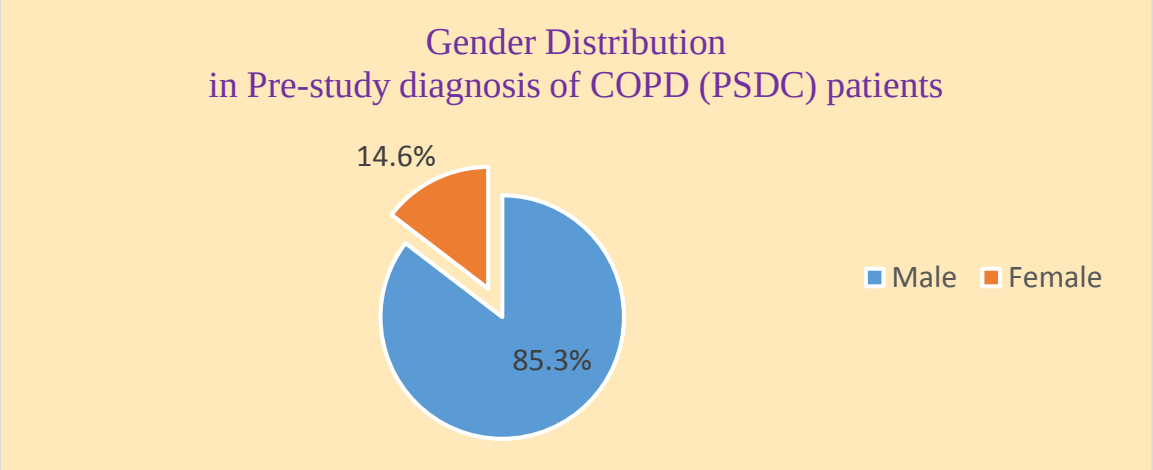


Figure 13 Gender breakup –PSDC COPD. N = 157

Among the 157 COPD patients who were included in the study majority of them were men (134, 85.3%). COPD is more commonly associated with men as smoking is less common among women.

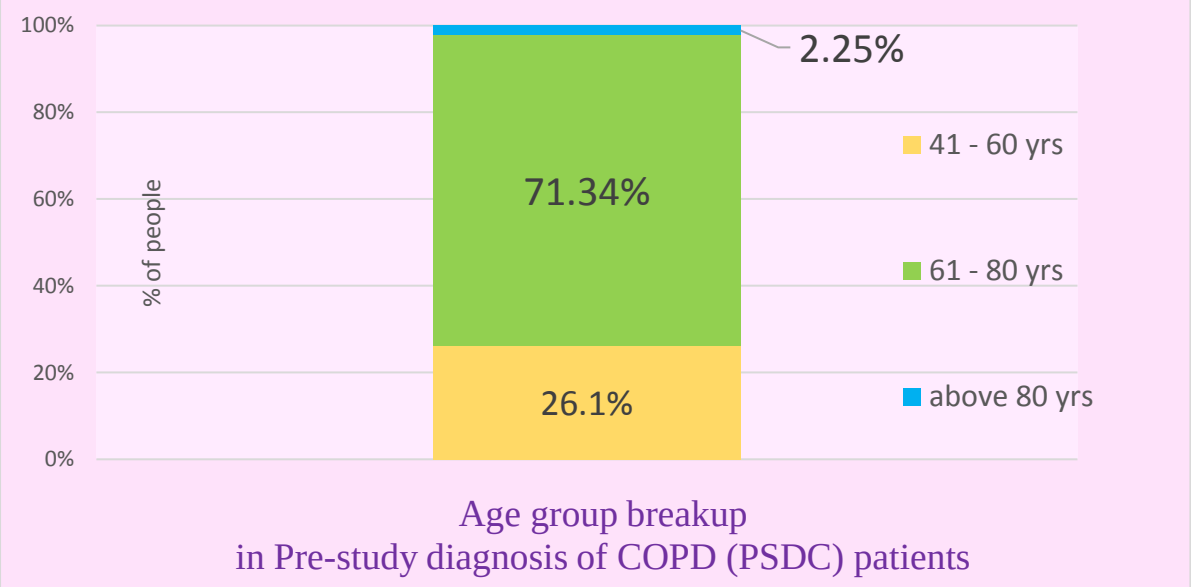


Figure 14 Age group breakup – PSDC COPD. N = 157

Most of the COPD patients were more than 60 years of age (71%). About 26.1% were between 40 - 60 years of age.

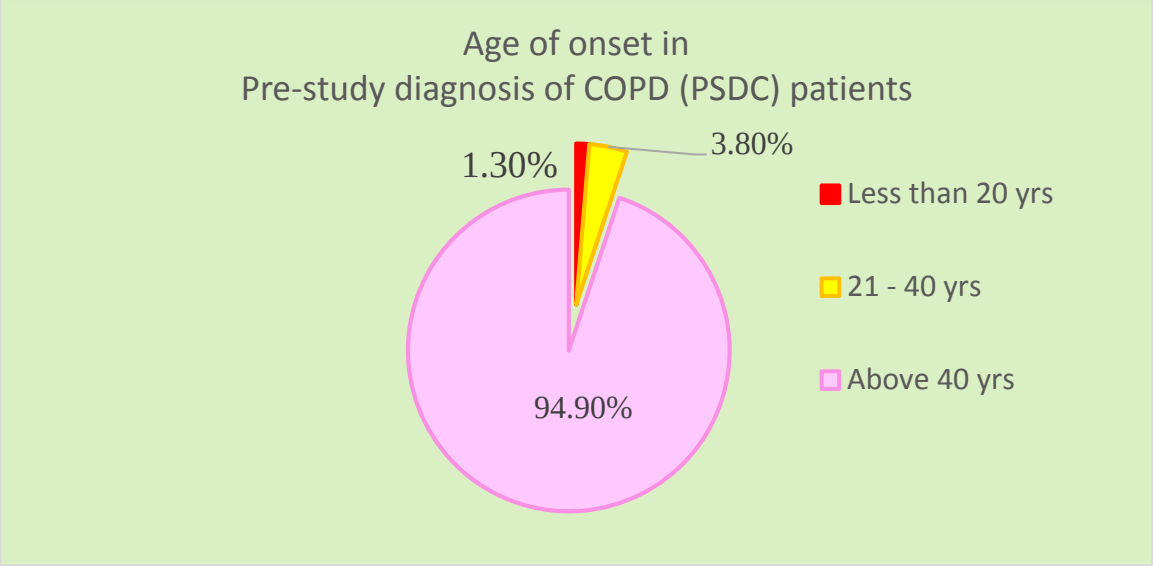


Figure 15 Age of onset Pre-study diagnosis of COPD (PSDC) patients. N = 157.

Most of the COPD patients developed the disease after 40 years of age: 149 (94.9%).

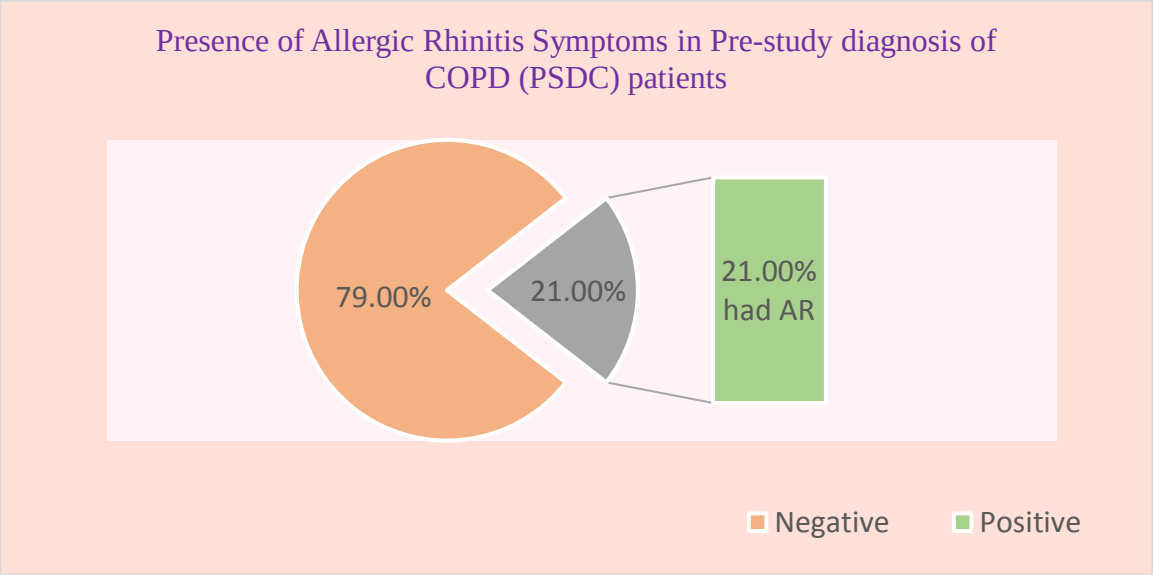


Figure 16 Presence of Allergic Rhinitis Symptoms in Pre-study diagnosis of COPD (PSDC) patients. N = 157

Although Allergic Rhinitis is a common finding in Asthma, it can be prevalent in certain cases of COPD patients as well (71–73). Only 21% of our PSDC had AR features.

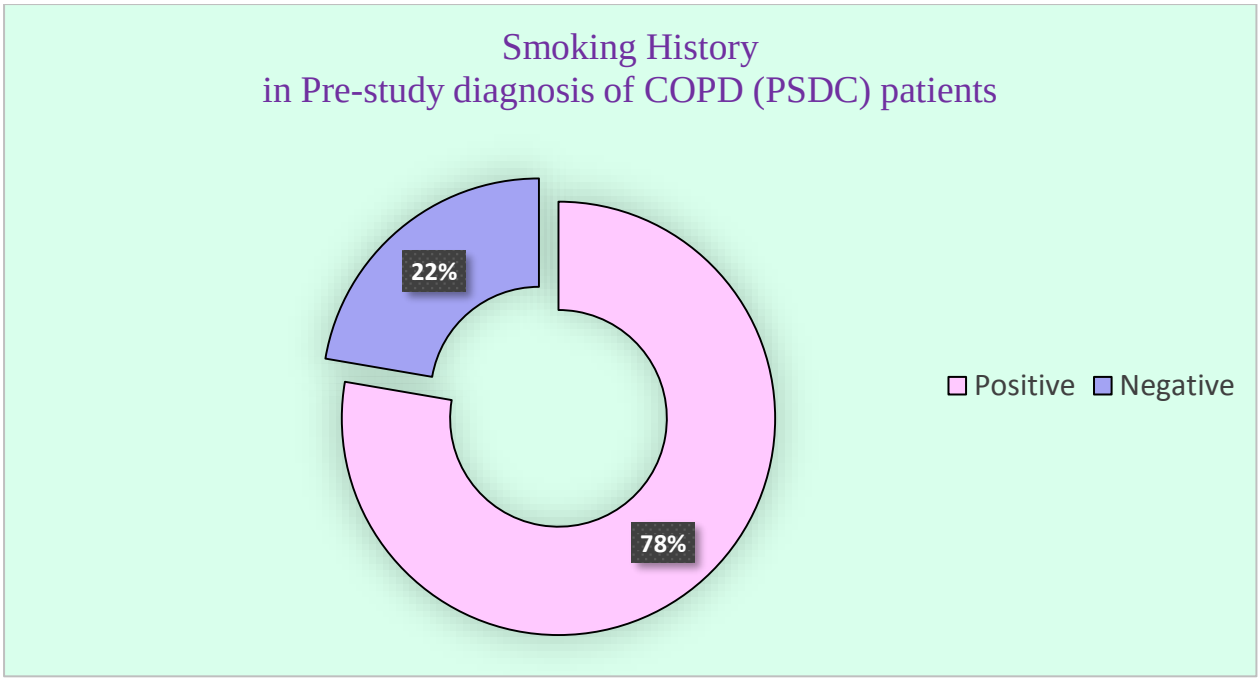


Figure 17 Smoking History in Pre-study diagnosis of COPD (PSDC) patients. N = 157

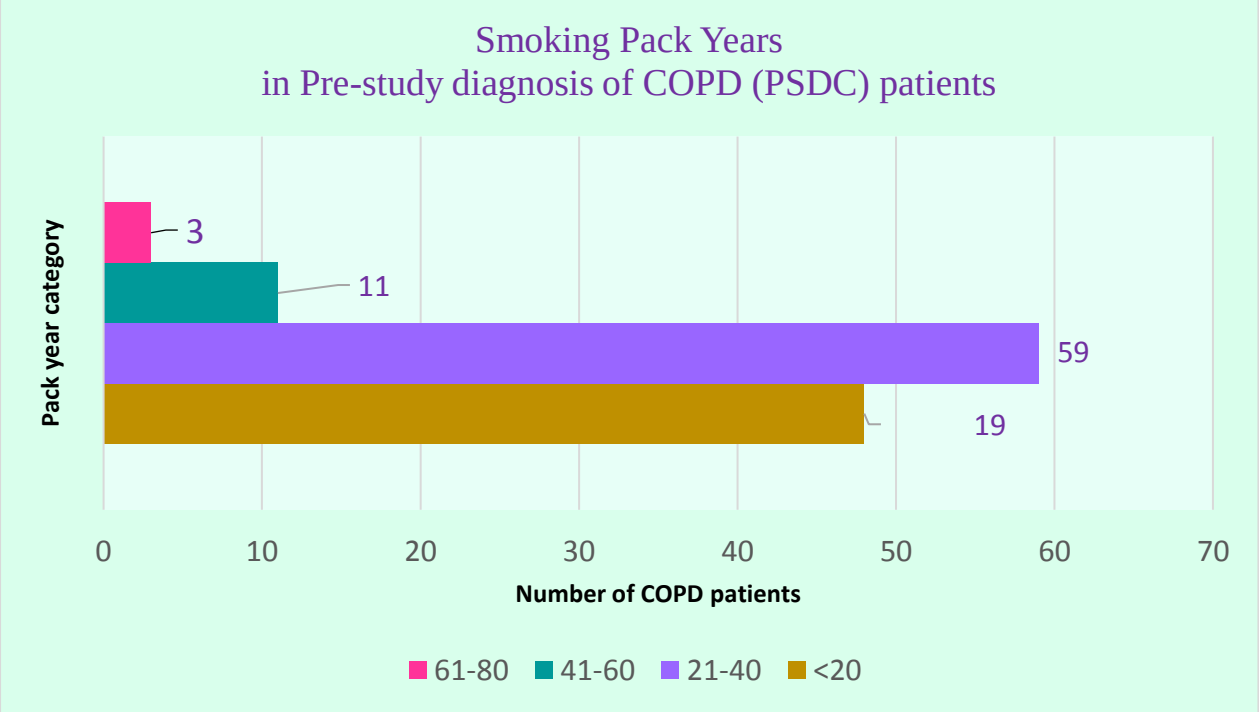


Figure 18 Pack years of smoking in PSDC COPD patients. N = 92, 78% of 157.

Of the 78 % smokers in the COPD group, 46% (73) of them had more than 20 pack years smoking history.

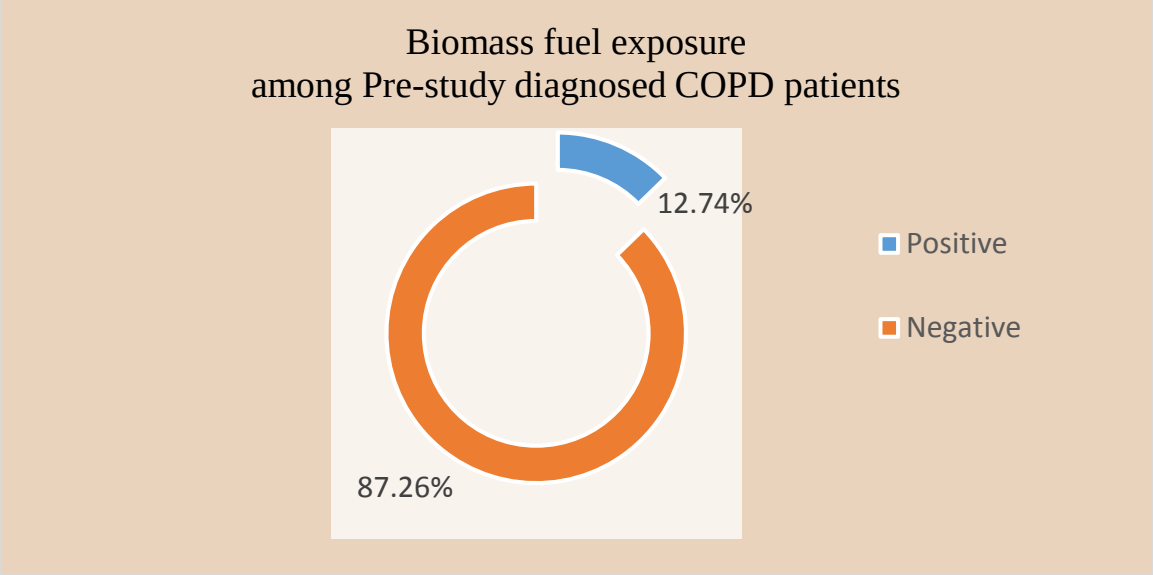


Figure 19 Biomass fuel exposure among Pre-study diagnosed COPD patients. N = 157

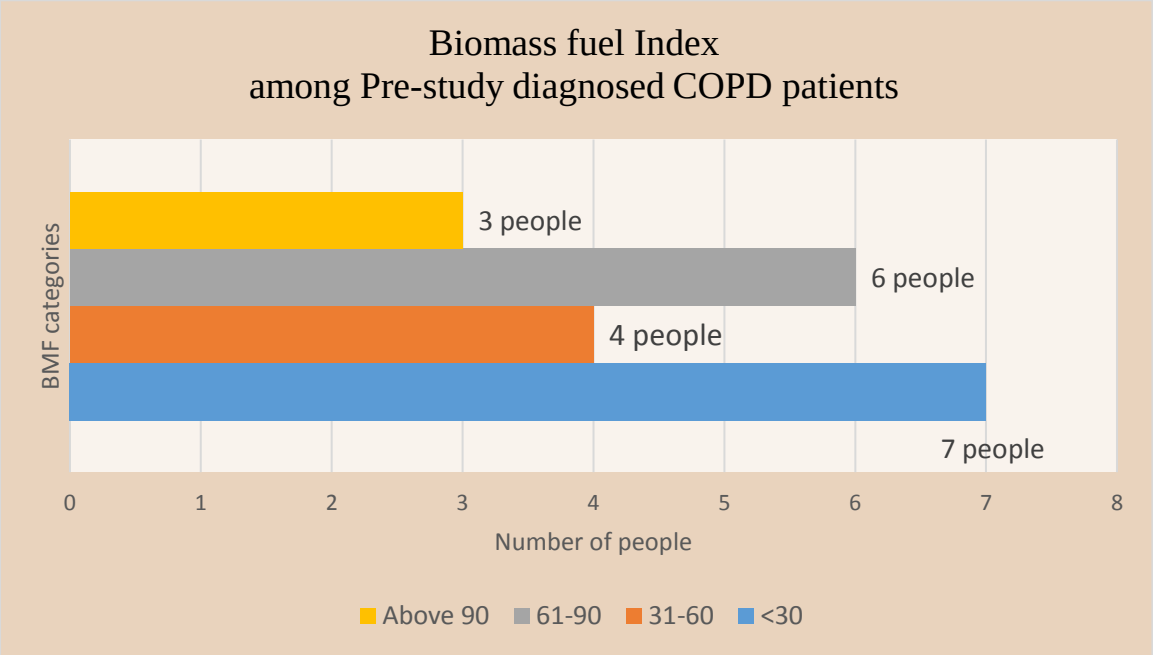


Figure 20 Biomass fuel Index among Pre-study diagnosed COPD patients. N = 20, 12.74% of 157.

Among COPD patients 13% of the patients were exposed to biomass fuel, and 6 % had significant BMF index.

Table 4: Treatment history in COPD

TREATMENT	TOTAL
SABA ONLY	2, (1.31%)
ICS LABA	18, (11.76%)
ICS LABA MONTELUKAST	2, (1.31%)
ICS LABA TIOTROPIUM	135, (85.98%)
TOTAL	157

Almost 85% of the COPD patients received triple therapy with Inhaled corticosteroids, long acting bronchodilators and anticholinergics.

Baseline Characteristics of the Pre-Study Diagnosis of Asthma patients who were reclassified as Confirmed Asthma, COPD and ACO based on the GINA-GOLD tool.

Among the 713 Pre-Study Diagnosis of Asthma (PSDA) patients who were enrolled in the study, after applying the GINA tool 681 (95.5%) patients had Confirmed Asthma, 12 (1.7%) had confirmed COPD and 20 (2.8%) had confirmed ACO. The following graphs and narratives summarizes the baseline characteristics among confirmed Asthma, confirmed COPD and confirmed ACO.

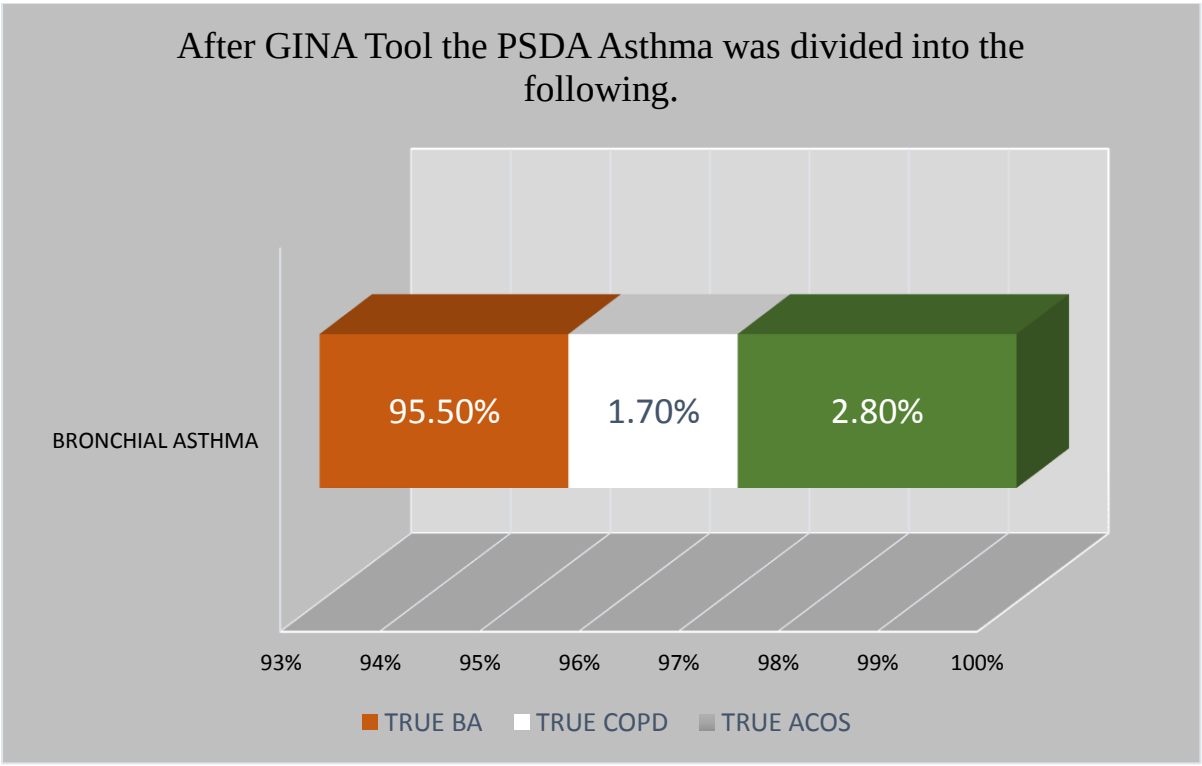


Figure 21 PSDA Asthma Reclassified into confirmed Asthma based on GIN-GOLD Tool. N is 713.

1) Gender distribution.

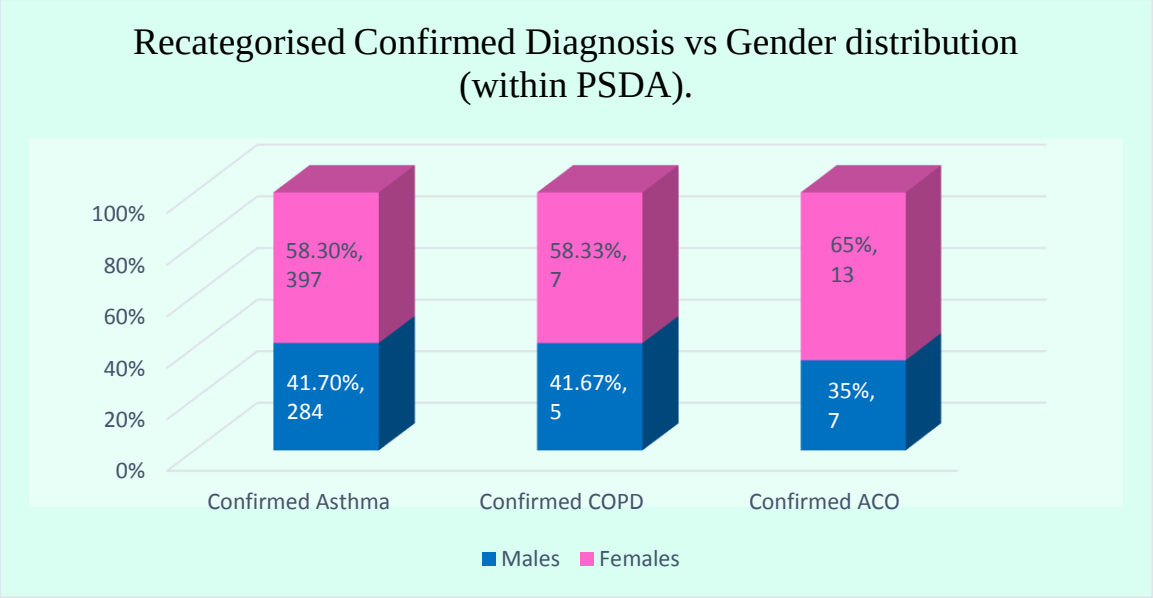


Figure 22 Recategorized Confirmed Diagnosis vs Gender distribution (within PSDA). N is confirmed Asthma 681, Confirmed COPD 12 and Confirmed ACO 20.

There were generally more number of women within the re categorized sub groups of PSDA. Among confirmed ACO, 65% were women.

2) Age group.

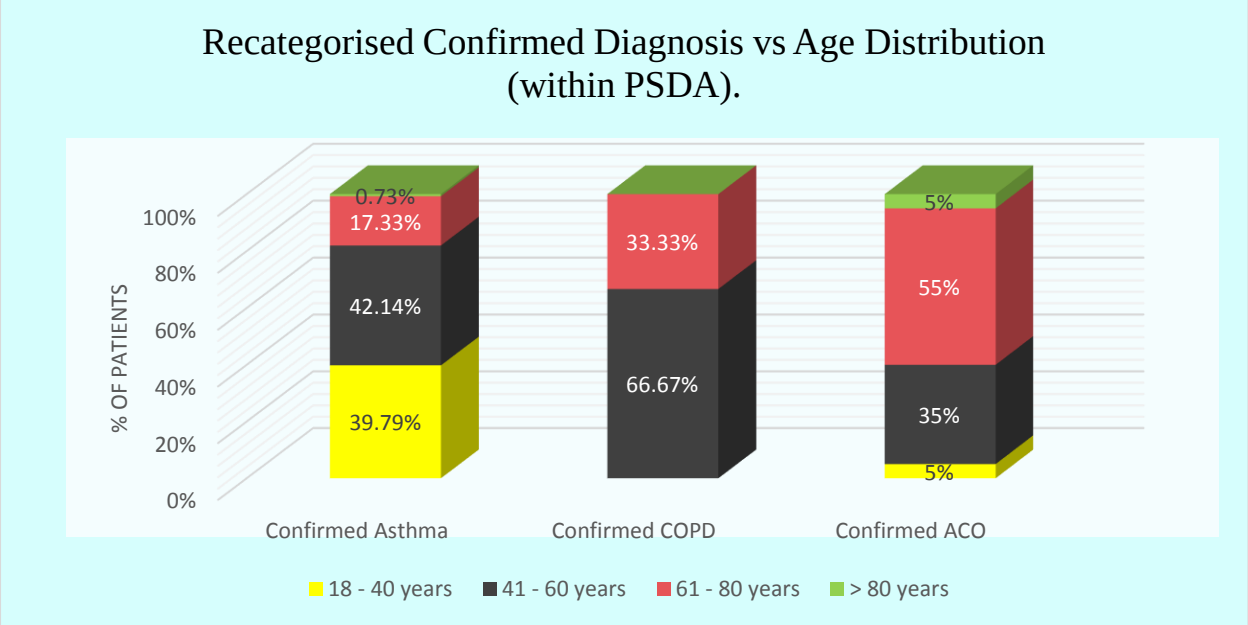


Figure 23 Recategorized Confirmed Diagnosis vs Age wise distribution (within PSDA). N is confirmed Asthma 681, Confirmed COPD 12 and Confirmed ACO 20.

Around 5% of confirmed ACO and 40% of confirmed Asthma are less than 40 years of age.

3) Age of onset of symptoms.

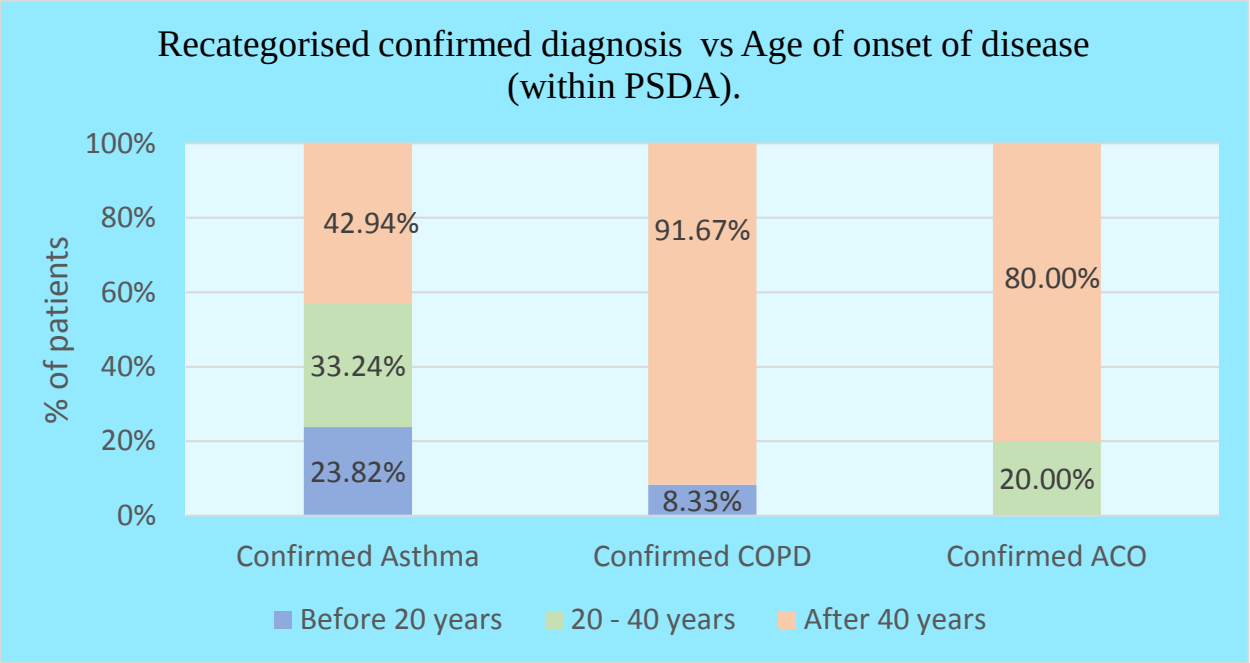


Figure 24 Recategorized Confirmed Diagnosis vs Age of onset of disease (within PSDA). N is confirmed Asthma 681, Confirmed COPD 12 and Confirmed ACO 20.

About 8.3% of the confirmed COPD patient from the Asthma pool had started having symptoms even before 40 years. A majority of 91.6% had onset of symptoms after 40 years.

Among confirmed Asthma patients 43% had onset of symptoms after 40 years compared to the 80% in ACO group.

Baseline characteristics of the Pre-Study Diagnosis of COPD patients who were reclassified as Confirmed Asthma, COPD and ACO based on the GINA-GOLD tool.

Among the 157, pre-study diagnosis of COPD (PSDC) patients who were enrolled in the study, after applying the GINA tool 39 (24.8%) patients had confirmed Asthma, 91 (58%) had confirmed COPD and 27 (17.2%) had confirmed ACO. This column summarizes the baseline characteristics among confirmed Asthma, confirmed COPD and confirmed ACO within PSDC.

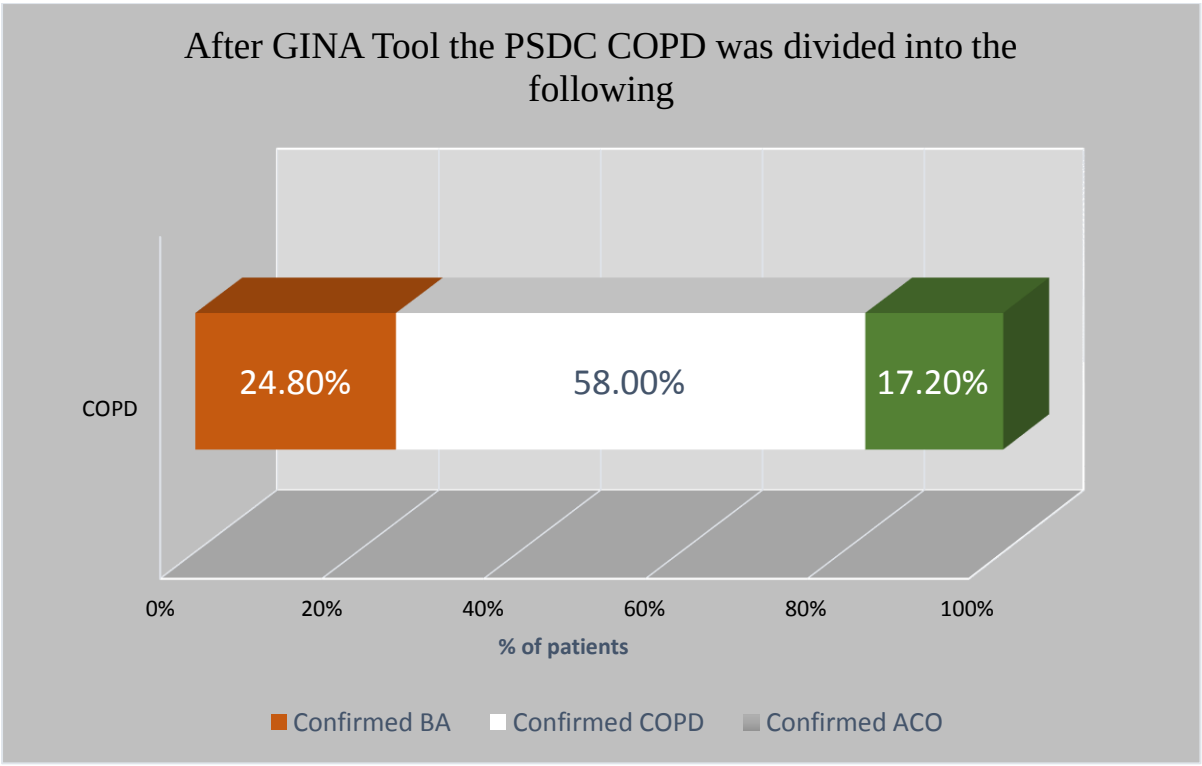


Figure 25 Reclassification of PSDC COPD based on the GINA-GOLD Tool. N is 157.

1) Gender distribution.

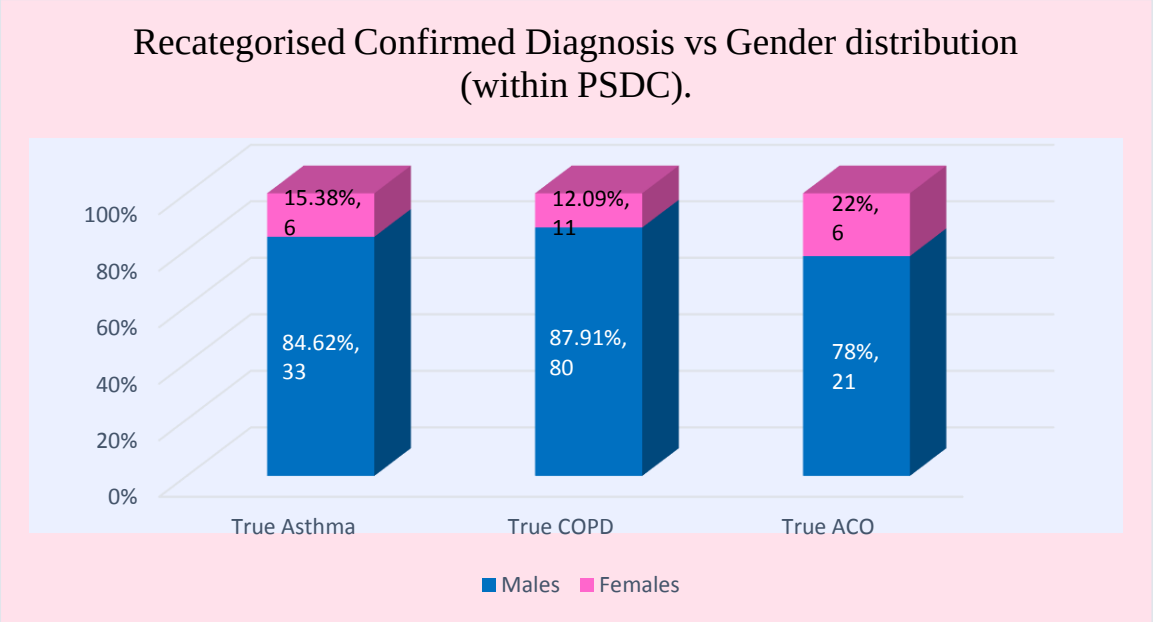


Figure 26 Recategorized Confirmed Diagnosis vs Gender distribution (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

In the PSDC pool, about 80% of each of confirmed Asthma, COPD and ACO are males.

2) Age group.

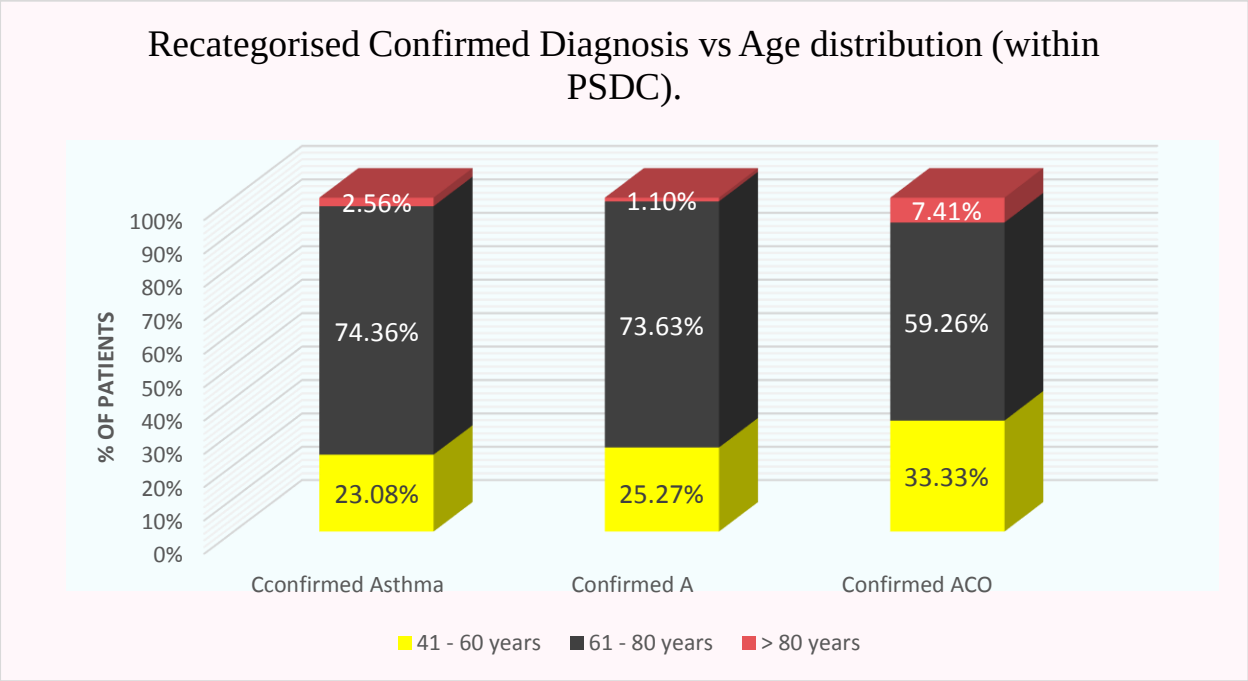


Figure 27 Recategorized Confirmed Diagnosis vs Age distribution (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

All of them were more than 40 years of age in PSDC pool. About (59%) confirmed ACO patients and (74%) of the confirmed Asthma were within the age group of 61 to 80 years of age.

3) Age of onset.

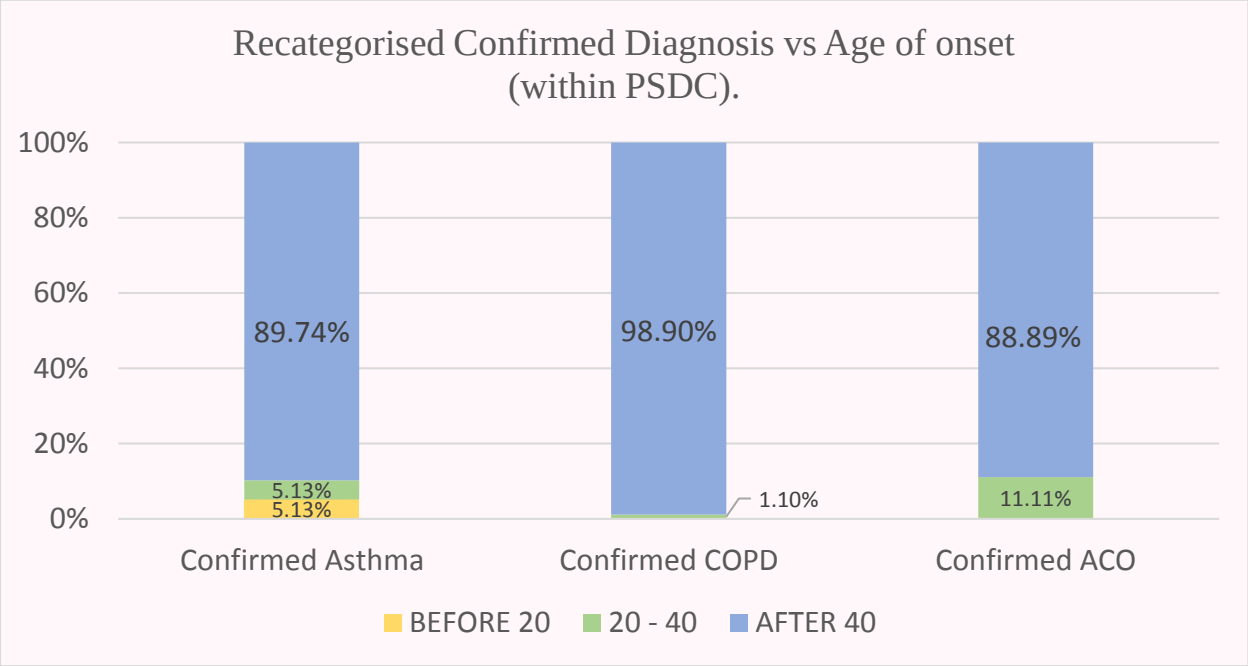


Figure 28 Recategorized Confirmed Diagnosis vs Age of symptoms onset (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

Up to 11% of ACO in the PSDC pool had onset of symptoms before 40. 90% of confirmed Asthma from the PSDC pool had onset of symptoms after 40.

4) History of Asthma in family,

None of the confirmed COPD patients from the PSDC pool had a positive family history of COPD, compared to the 15% in confirmed Asthma patients.

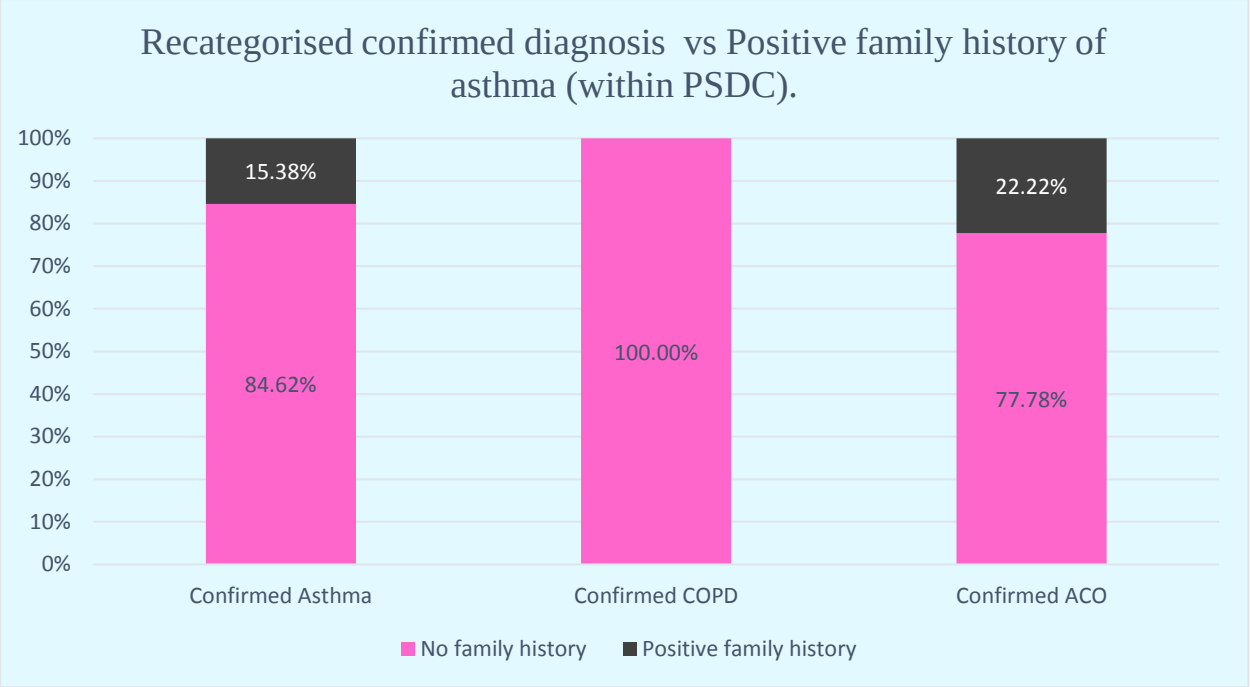


Figure 29 Recategorized Confirmed Diagnosis vs +ve family history (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

5) History suggestive of Allergic Rhinitis.

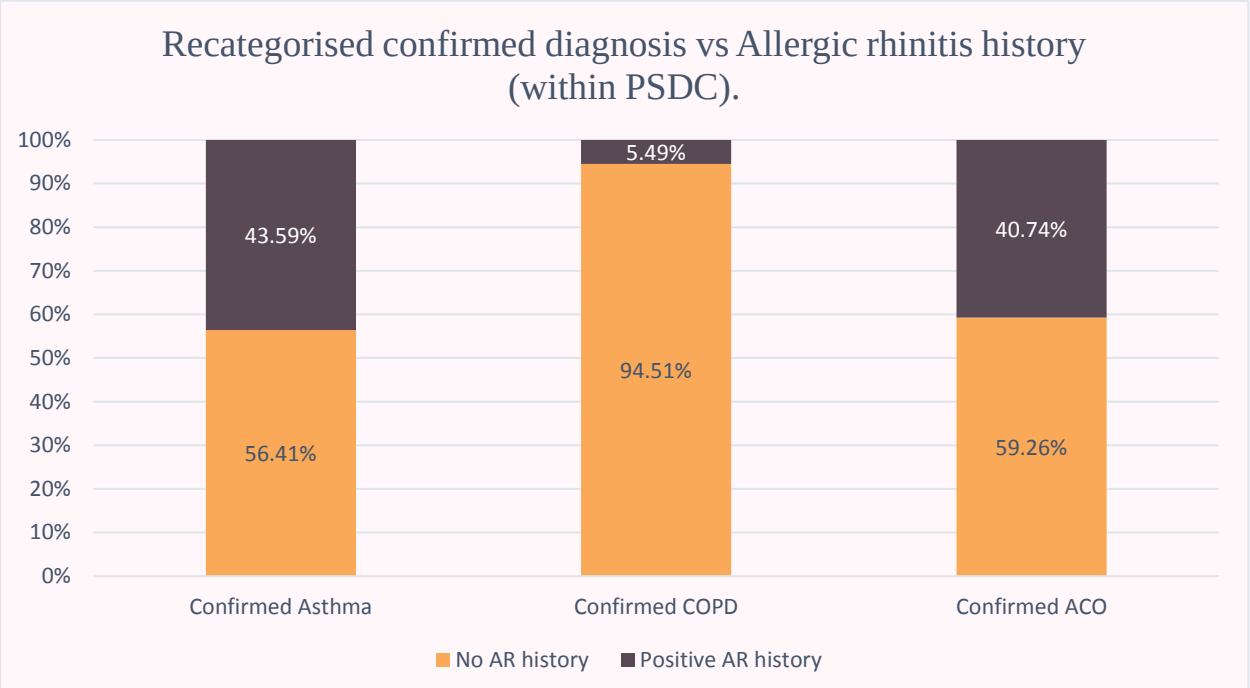


Figure 30 Recategorized Confirmed Diagnosis vs AR history (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

Up to 43% of confirmed Asthma and 41% of confirmed ACO had positive Allergic Rhinitis history in PSDC pool compared to 5% among confirmed COPD.

6) Spirometry.

1. Presence of obstruction,

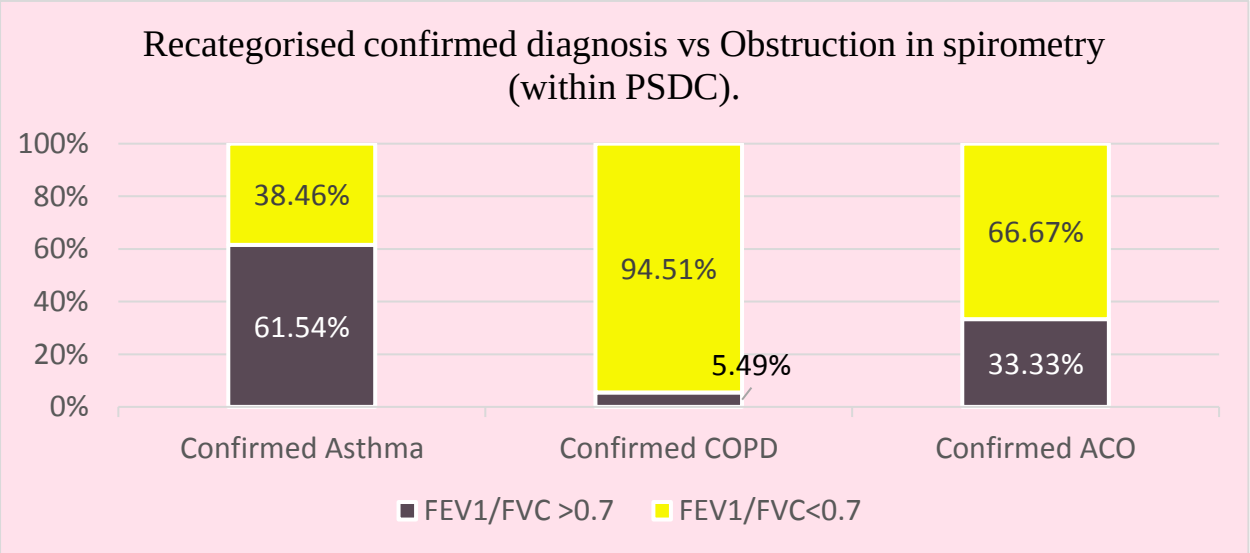


Figure 31 Recategorized confirmed diagnosis vs Obstruction in spirometry (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

2. Reversibility of obstruction in spirometry.

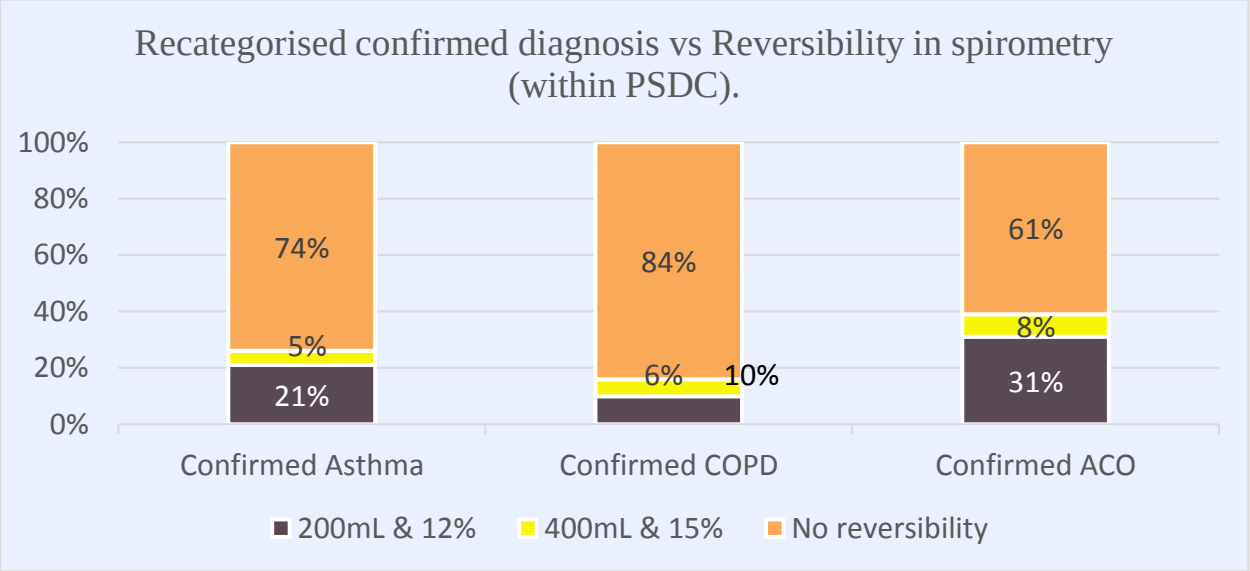


Figure 32 Recategorized confirmed diagnosis vs Reversibility in spirometry (within PSDC). N is True Asthma 39, True COPD 91 and True ACO 27.

In the PSDC pool 62% of the confirmed Asthma patients and 33% of the confirmed ACO patients had no obstruction. More over 16% of the confirmed COPD patients still had reversibility in the spirometry.

Pre-Study Diagnosis of Asthma-COPD overlap group.

The concept of ACO was present even before GINA guidelines were setup. Hence there were a few ACO patients who were clinically diagnosed. They were included in the study to assess if the diagnosis was correct. Totally 7 ACO patients were included. Of them 5 turned out to be Asthma, 1 COPD and 1 was truly ACO. This reemphasizes the need for a universal accepted criterion to diagnose ACO. It is also to be kept in mind that not all Asthmatic smokers are ACO.

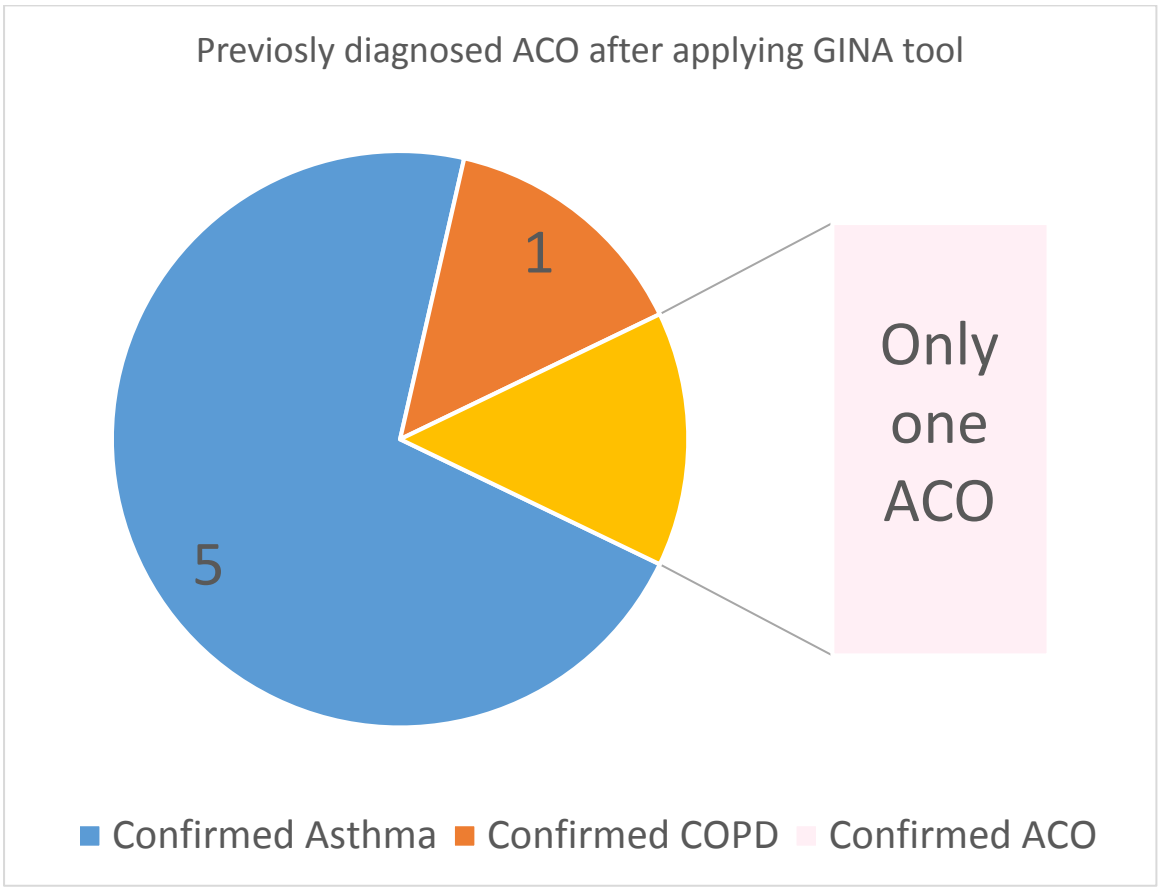


Figure 33 Previously diagnosed ACO after recategorization based on GINA-GOLD tool. N = 7

Study results after re categorizing diagnosis (as per GINA-GOLD syndromic approach tool)

The total number of Pre-study diagnosis of Asthma patients were 713 and the number pre-study diagnosis of COPD patients were 157. 7 patients who had a pre-study diagnosis of ACO based on some other criteria were also included to verify their diagnosis.

At the end of the study the number of Confirmed ACO patients went up to 48 out of 877, which was 5.4% of the entire study population. The number of Confirmed Asthma patients increased, as a lot of pre-study diagnosis COPD and ACO patients turned out to be confirmed Asthma at the end of the study.

Of the 713 pre-study asthma patients, only 681 (96%) of them were confirmed as asthmatics. 12 (1.7%) were confirmed to be COPD and 20(2.3%) were confirmed to be ACO.

Likewise of the 157, pre-study diagnosis of COPD patients who were enrolled in the study, only 91 (58%) were confirmed COPD, 39 (25%) of them turned out to be confirmed Asthma patients and 27 (17%) of them were confirmed ACO patients.

There were 7 ACO patients who were also included in the study to verify the diagnosis according to GINA-GOLD syndromic approach guidelines, however only one of them was confirmed to be ACO, 5 of them were confirmed as Asthma and 1 of them was confirmed to be COPD.

Table 5: Tabulation of Initial diagnosis against Final diagnosis.

PRE-STUDY DIAGNOSIS	CONFIRMED DIAGNOSIS			TOTAL
	ASTHMA	COPD	ACO	
ASTHMA	681	12	20	713
	93.93	11.54	41.67	81.30
COPD	39	91	27	157
	5.38	87.50	56.25	17.90
ACO	5	1	1	7
	0.69	0.96	2.08	0.80
	725	104	48	877

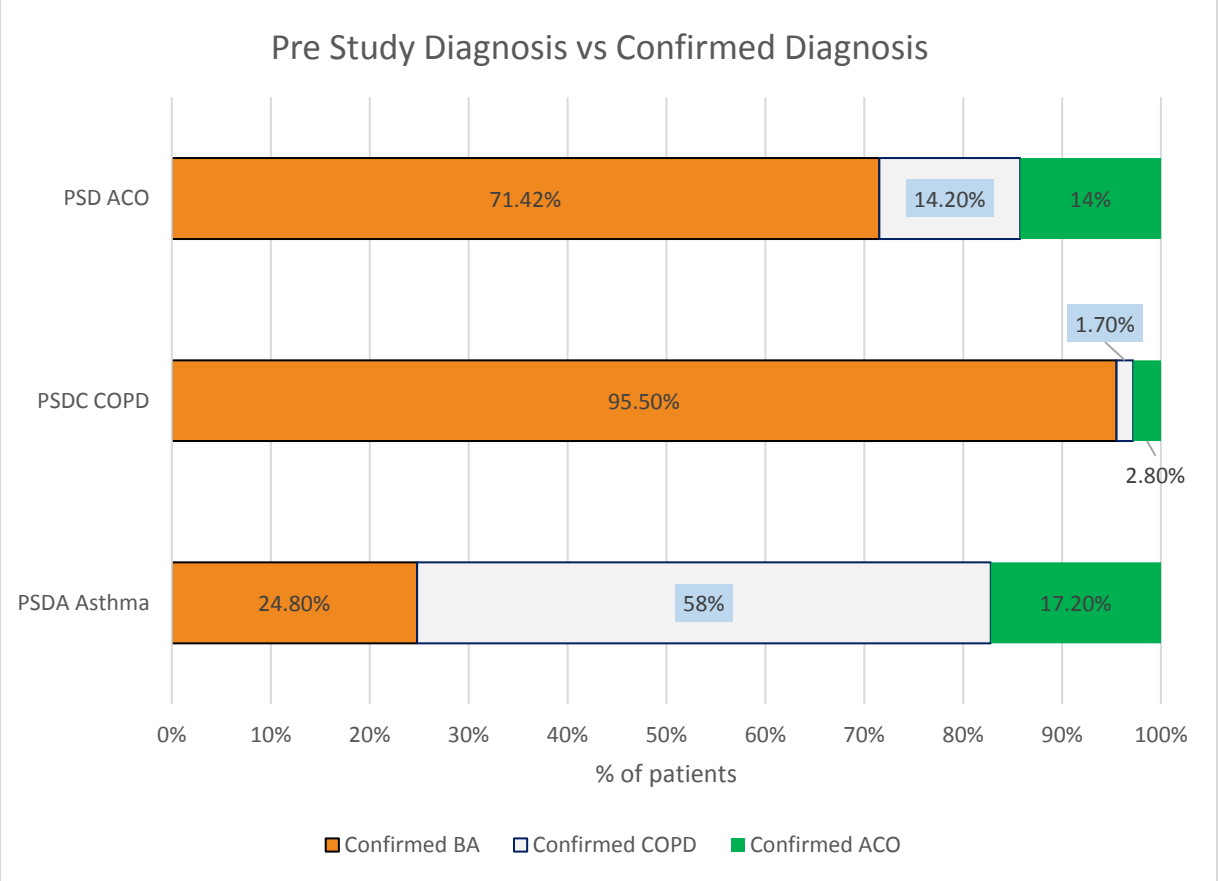


Figure 34 Comparison of Confirmed Diagnosis vs Pre-study diagnosis. N= 877.

Comparison of confirmed cases of Asthma, COPD and ACO.

Gender distribution

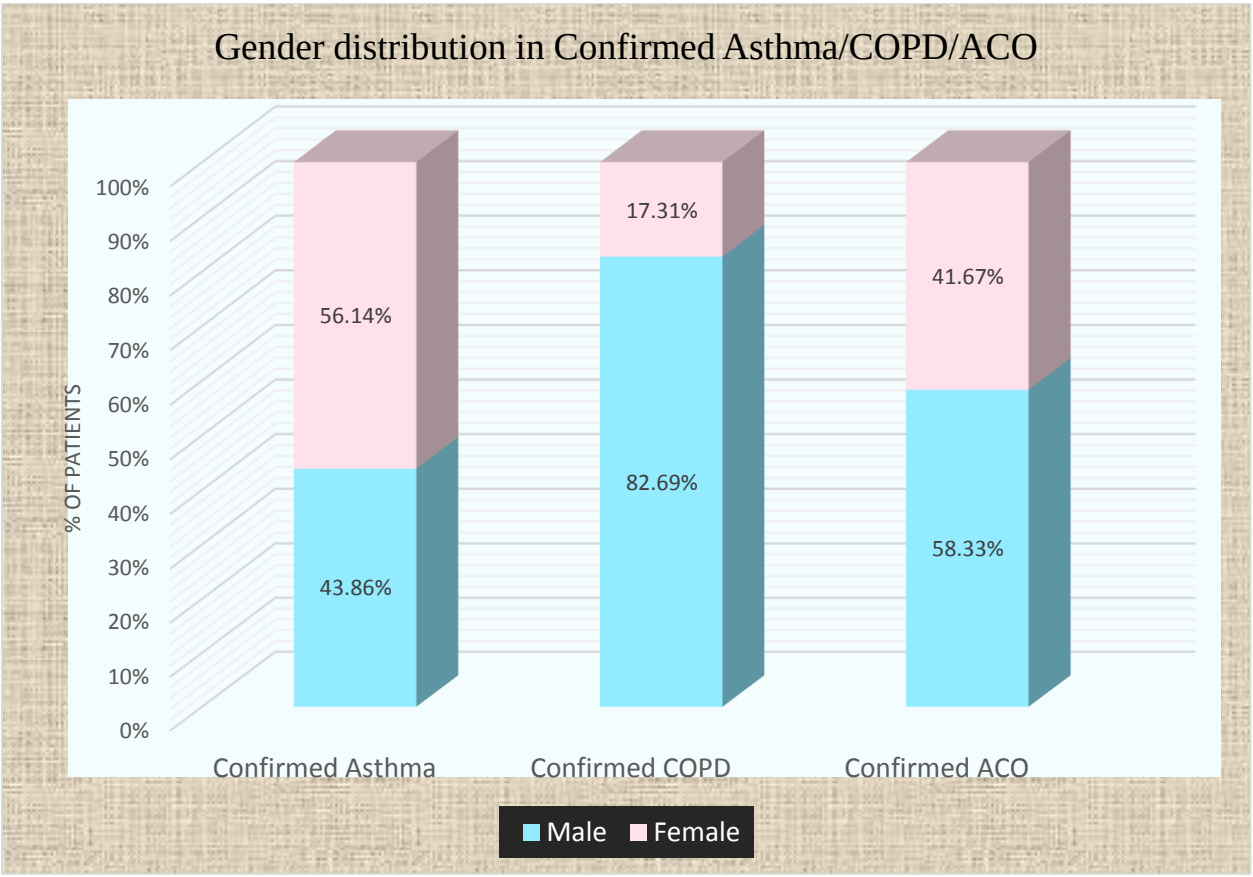


Figure 35 Gender distribution in Confirmed Asthma/COPD/ACO. N: *877*

The number of males in both COPD and the ACO group were higher compared to the females. Whereas the number of females in the asthma group was higher. The gender distribution in asthma and COPD is similar to existing literature.

Age distribution of Confirmed Asthma, COPD and ACO.

The prevalence of Asthma was mostly in the younger age groups compared to COPD and ACO. The number of COPD and ACO patients in the 60+ age group was almost double the number in the 40 – 60 age group. The mean age of patients in each of the groups is as follows: Asthma 46 ± 15, COPD 64 ± 9 and ACO 62 ± 11.

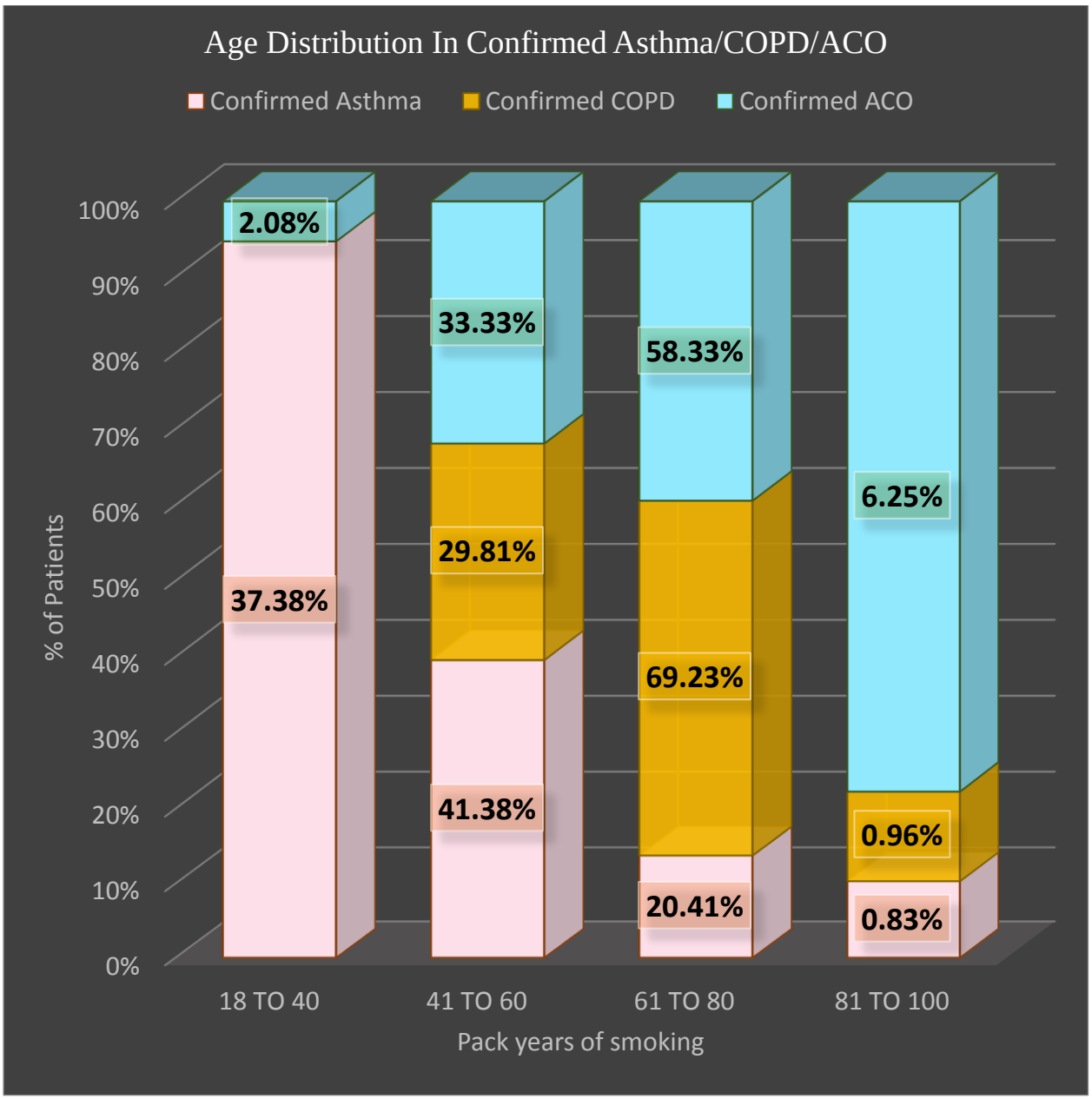


Figure 36 Age Distribution in Confirmed Asthma/COPD/ACO. N = 877.

Smoking history in Confirmed Asthma, COPD and ACO.

Both smoking and Biomass fuel exposure are associated with COPD and ACO. The total number of smokers were more in the COPD group (77%) and ACO group (50%) compared to Asthma group (7%).

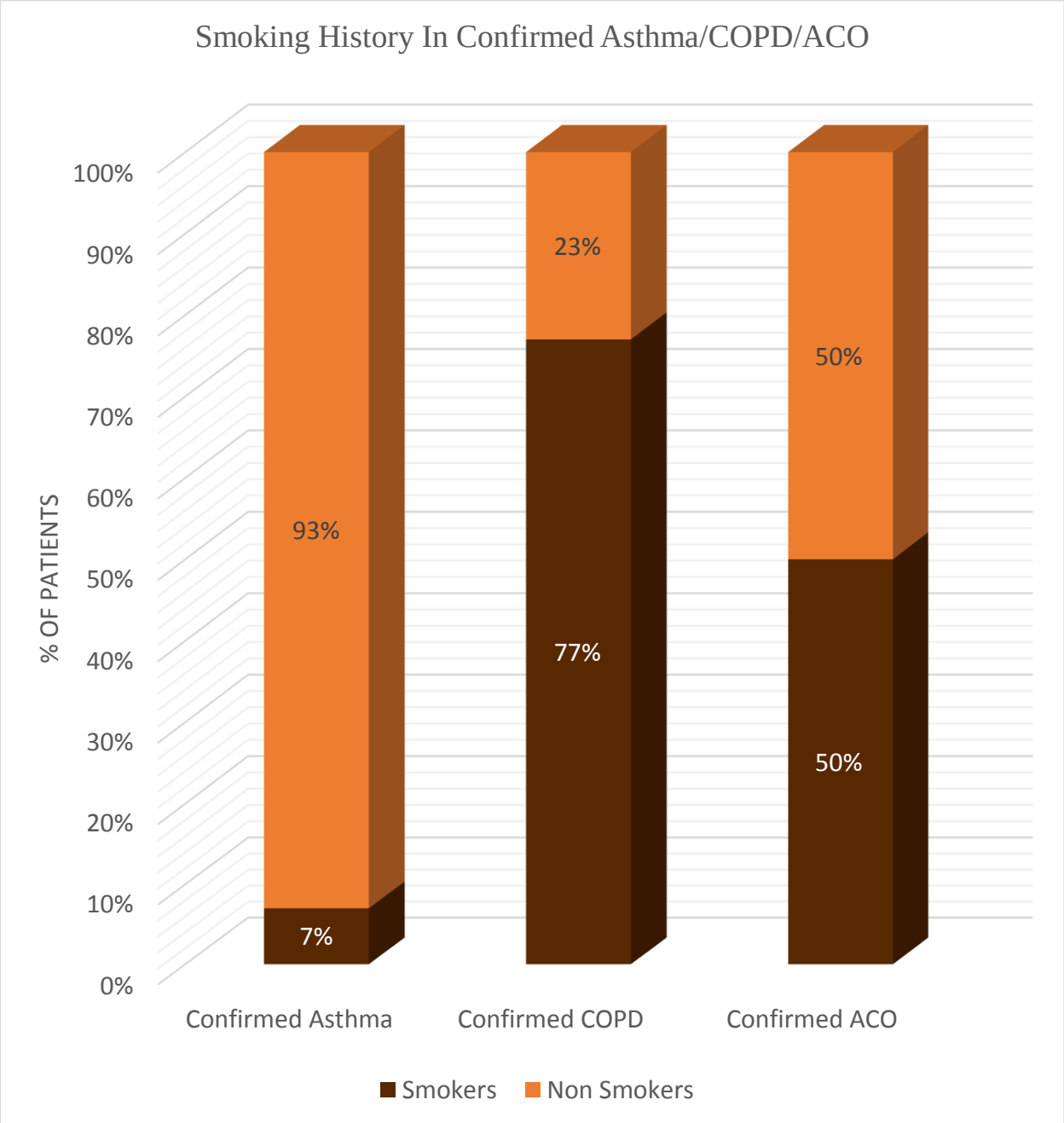


Figure 37 Smoking History in Confirmed Asthma/COPD/ACO. N = 877.

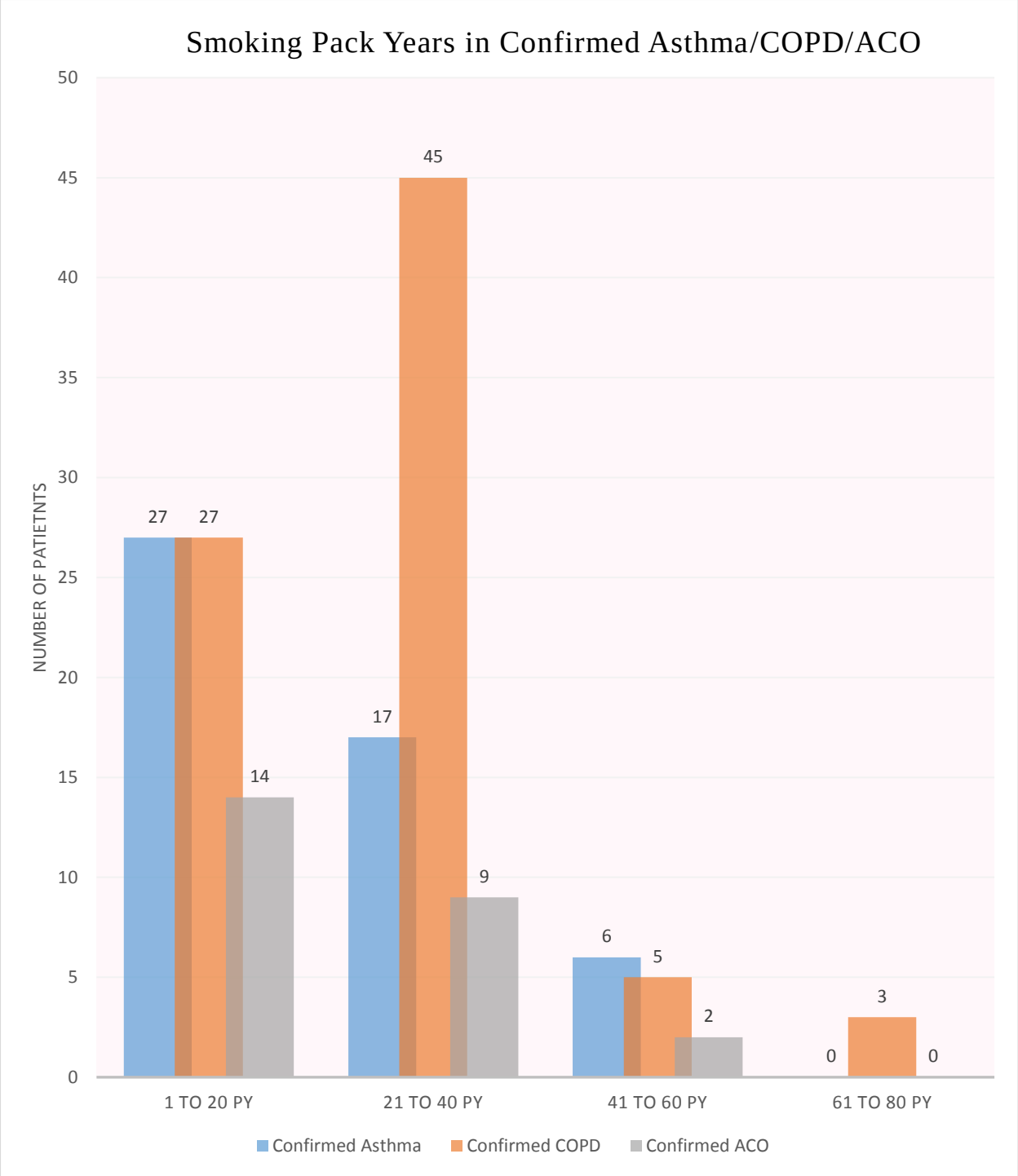


Figure 38 Smoking Pack Years in Confirmed Asthma/COPD/ACO. N is confirmed cases of Asthma = 50, COPD = 80, ACO = 25.

Most patients were smoker of 21 to 40 pack years. 50 % of COPD patients had more than 20 pack years. 26% of COPD patients had less than 20 Pack years. Among the patients who smoke in ACO, 56% (14) had less than 20 pack years.

Biomass fuel exposure history in Confirmed Asthma, COPD and ACO.

Not all COPD patients were smokers. Smoking was more common among the male COPD patients. 16% of all COPD smokers were exposed to biomass fuel exposure, who were all mostly females (99%). The proportion of BMF exposure amongst asthma was 23% and ACO was 37%, most of them were females.

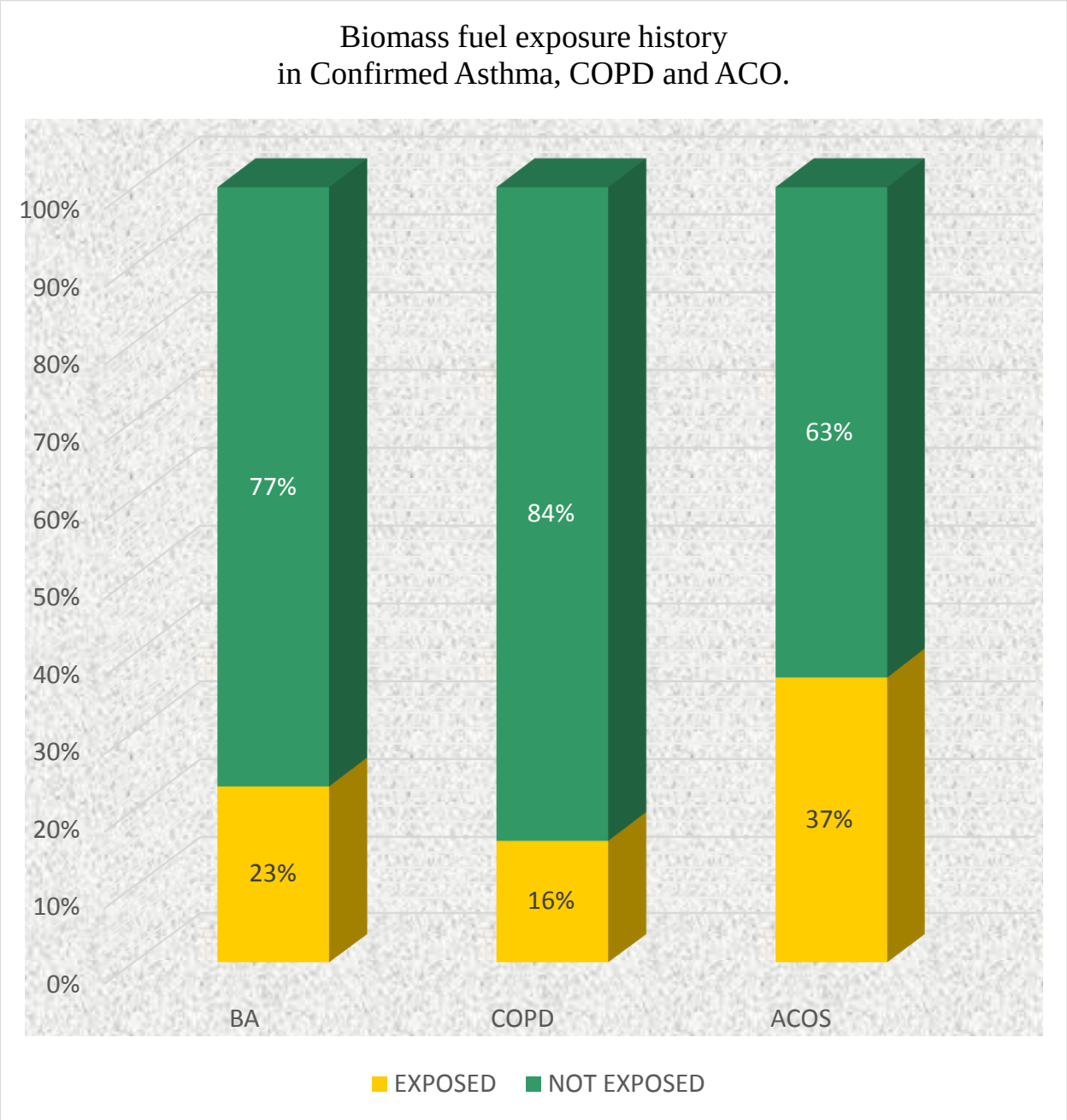


Figure 39 Biomass fuel exposure history in Confirmed Asthma, COPD and ACO. N = 877.

Biomass exposure index is defined as average number of hours of cooking every day multiplied by the total no of years of cooking by that individual. A high BMF index of 60 hr*yrs was observed in ACO (18%), compared to COPD (3.8%) and asthma (2.4%).

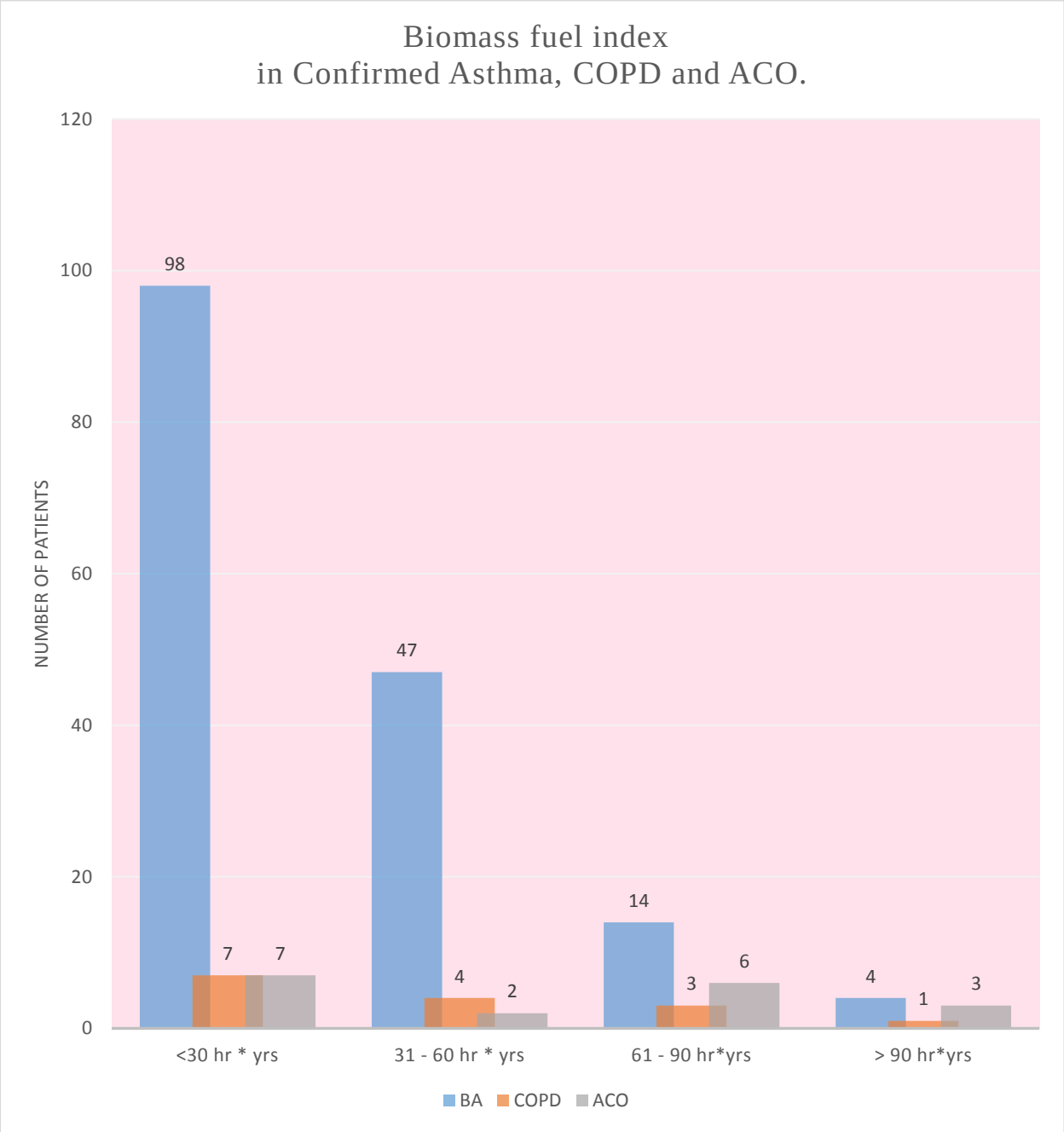


Figure 40 Biomass fuel index in Confirmed Asthma, COPD and ACO. N is confirmed case of Asthma =163, COPD =15, ACO =18.

History of AR and family h/o Asthma in Confirmed Asthma, COPD & ACO.

Only 29% of asthma patients had a family history of Bronchial Asthma. 1% of COPD patients also had a family history of Asthma but they were smokers with significant smoking pack years. 25% of all ACO patients also had family history of bronchial asthma.

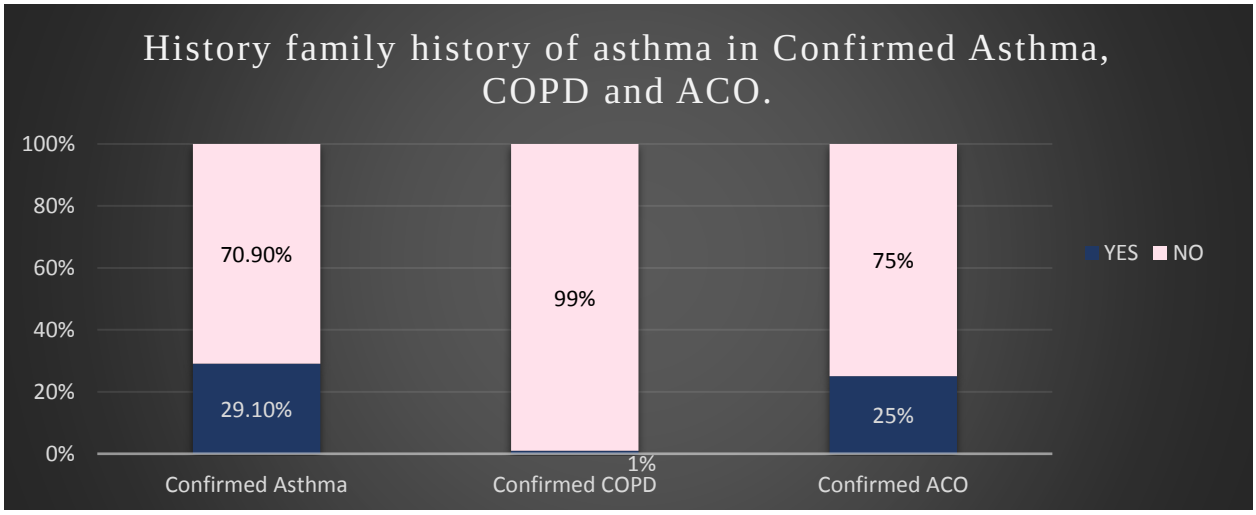


Figure 41 History family history of asthma in Confirmed Asthma, COPD and ACO. N = 877

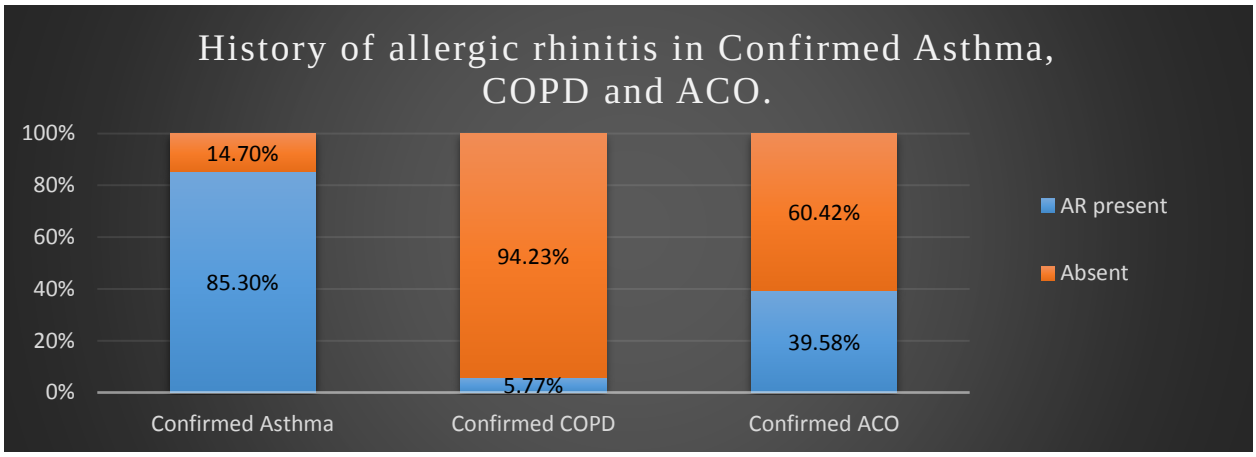


Figure 42 History of allergic rhinitis in Confirmed Asthma, COPD and ACO. N = 877

A whopping 85% of true asthma patients had features suggestive of allergic rhinitis. Similarly 39% of ACO patients and <1% of COPD patients also had a positive history for allergic rhinitis.

Spirometry:

Among confirmed COPD, 5.7% of had no obstruction in spirometry and 35.42% of the patients diagnosed as ACO also had no obstruction.

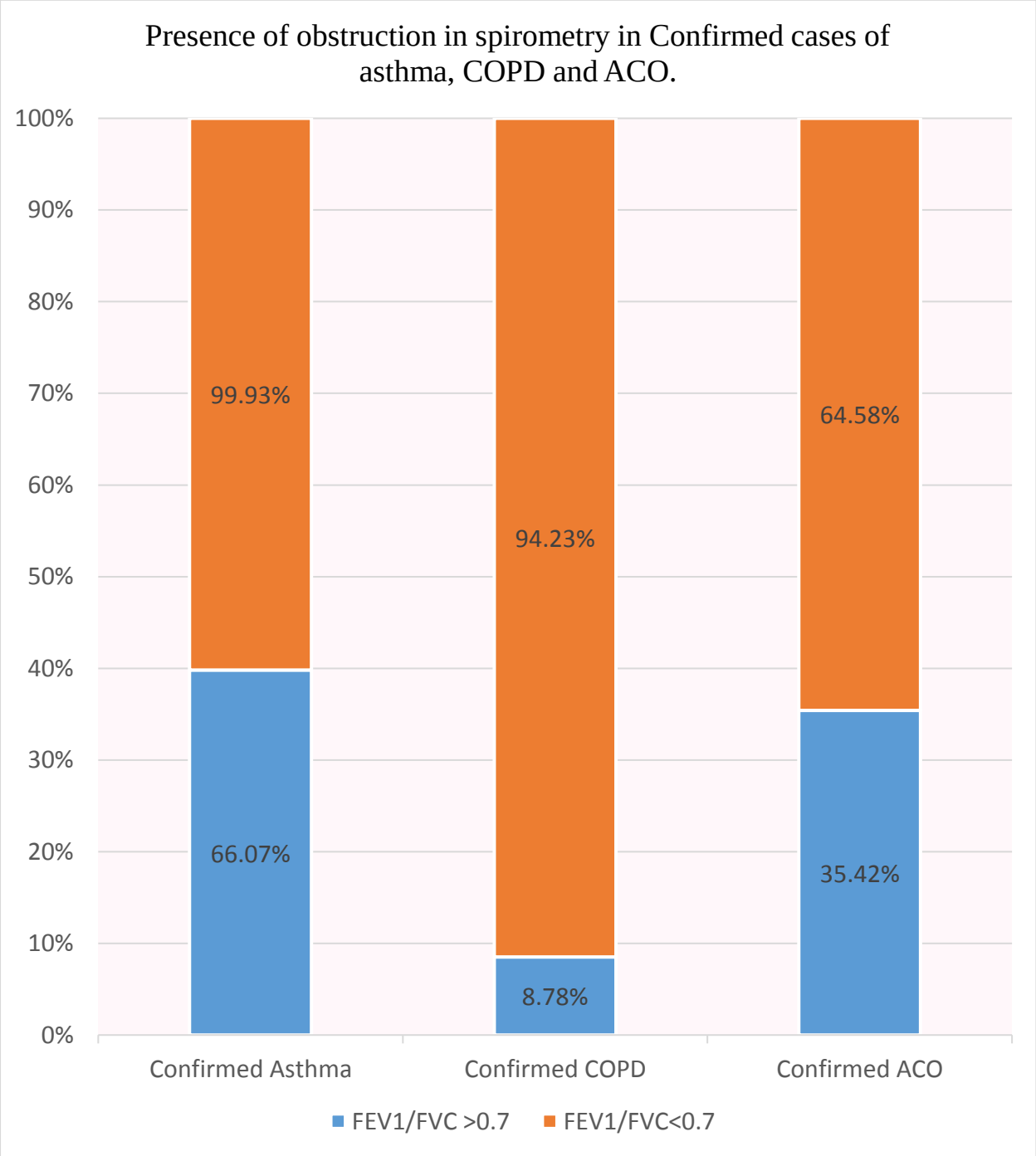


Figure 43 Presence of obstruction in spirometry in Confirmed cases of asthma, COPD and ACO. N = 877.

A significant proportion of COPD and ACO patients fell into the severe and very severe obstruction group. Most asthma patients had mild and moderate obstruction.

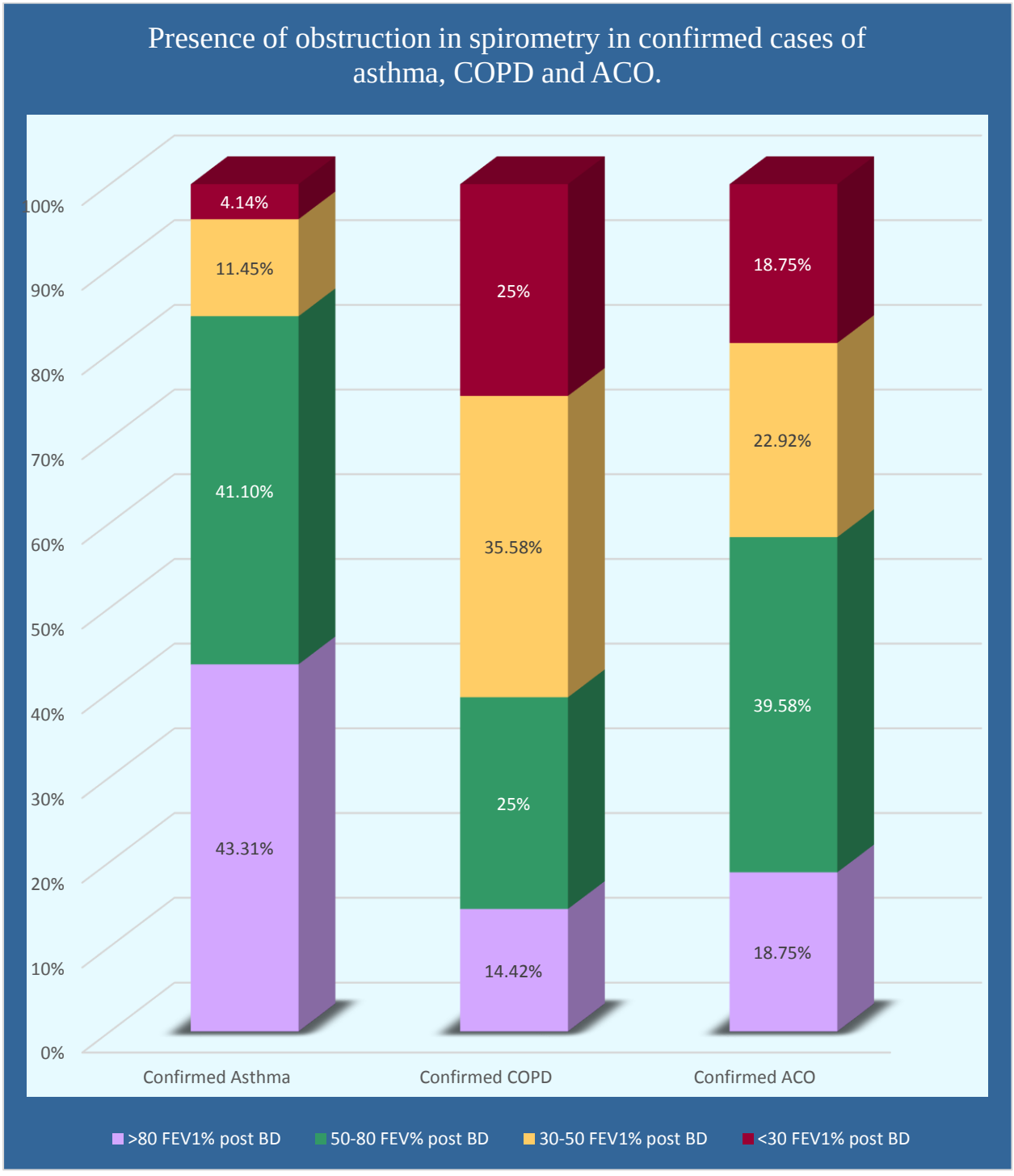


Figure 44 Severity of obstruction in spirometry in Confirmed cases of asthma, COPD and ACO. N = 877.

Significant reversibility of obstruction after bronchodilator administration is a unique characteristic of Asthma. However, reversibility can be present in severe and very severe obstructive cases of COPD and ACO. Even among asthmatics after commencement of treatment a reversible component or an obstruction can be absent. All the available spirometry reports of the study patients were analyzed and the one with the maximum reversibility was considered for this analysis.

Eighteen percent of confirmed COPD patients and 32% of confirmed ACO patients have shown reversibility. Of which the 400ml & 12% reversibility, that is almost diagnostic of asthma was also present in 6 confirmed COPD and 2 confirmed ACO patients. This again could be explained by the presence of overlap symptoms.

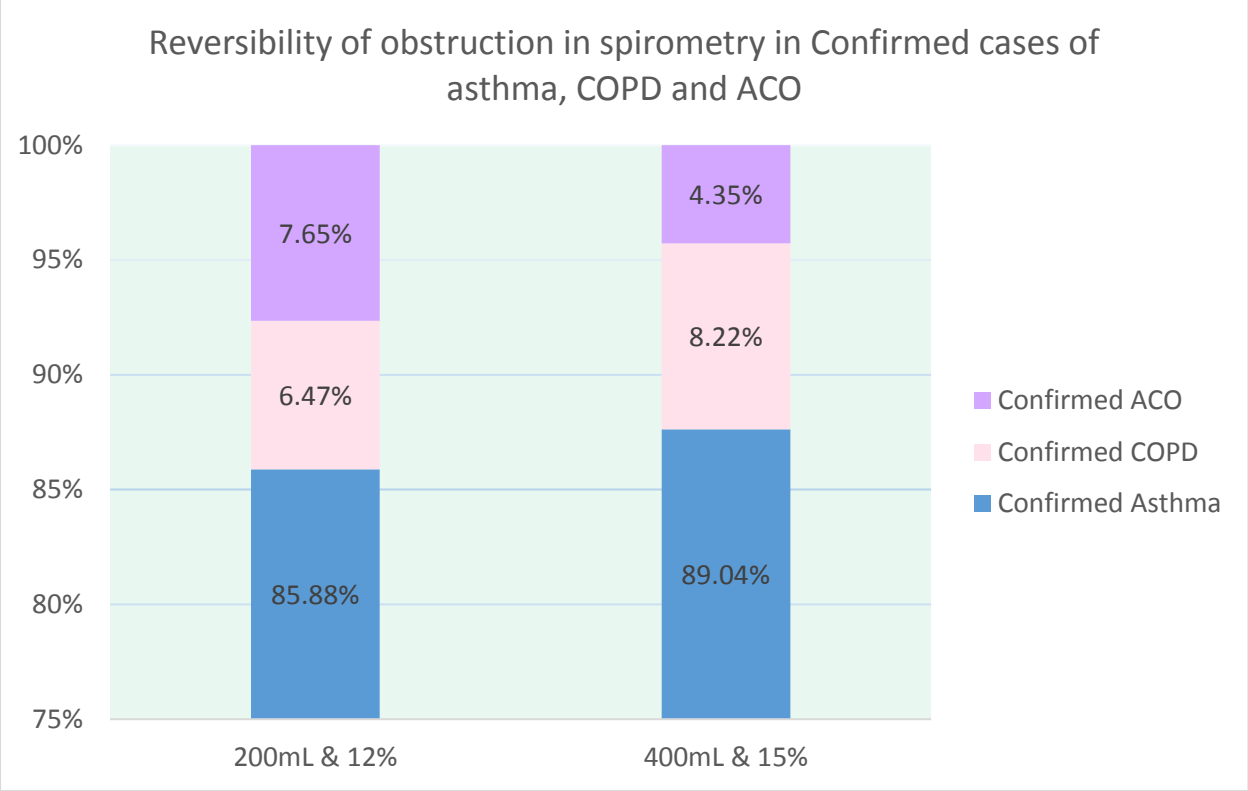


Figure 45 Reversibility of obstruction in spirometry in Confirmed cases of asthma, COPD and ACO. N is patients with reversibility 200ml and 12% is 170, 400 ml and 15% is 73.

Chest X ray comparison in confirmed cases of Asthma, COPD and ACO.

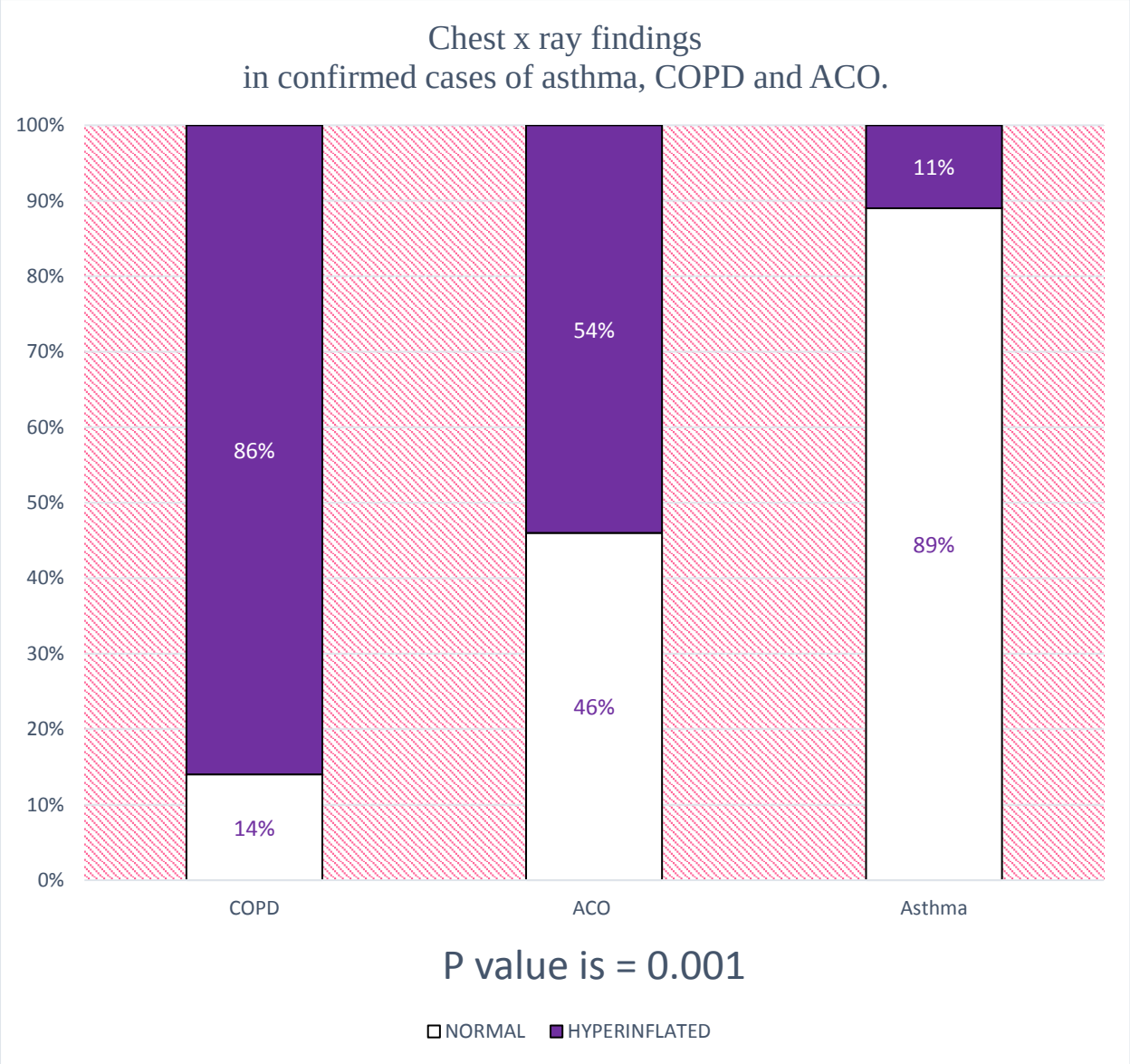


Figure 46 Chest x ray findings in confirmed cases of asthma, COPD and ACO. N = 877

Confirmed COPD (86%) and confirmed ACO (54%) had hyperinflation on Chest X ray compared to (11%) of confirmed asthma patients. Severe hyperinflation on an X ray predicts worse effort tolerance and more symptoms.

Six-minute walk desaturation in confirmed cases of Asthma, COPD and ACO:

Exertional desaturation was more common in COPD 33% followed by ACO 12%. Only 6% of asthmatics had significant desaturation. More than 4% desaturation was considered significant desaturation in a COPD patient. (74,75)

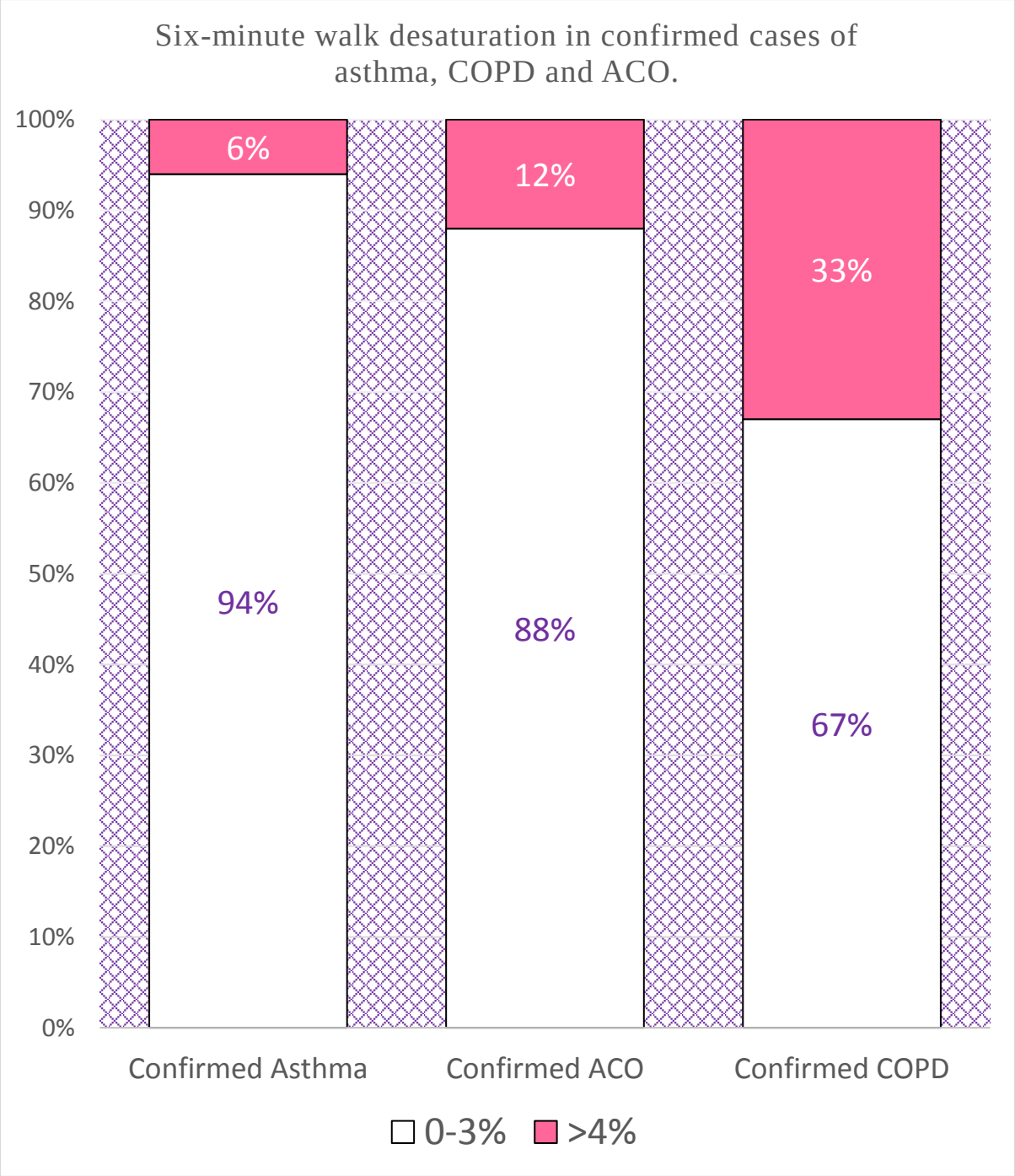


Figure 47 Six-minute walk desaturation in confirmed cases of asthma, COPD and ACO. N = 877

Distance saturation Product in confirmed cases of Asthma, COPD and ACO.

Distance saturation product in COPD is known to be lower corresponding to the drop-in saturation with exertion. Comparing confirmed Asthma and COPD, the latter has -63m% worse DSP with a p value of 0.003. Likewise comparing confirmed ACO with COPD the former has +50m% better DSP than COPD. DSP is more decreased in confirmed COPD compared to Asthma or ACO.

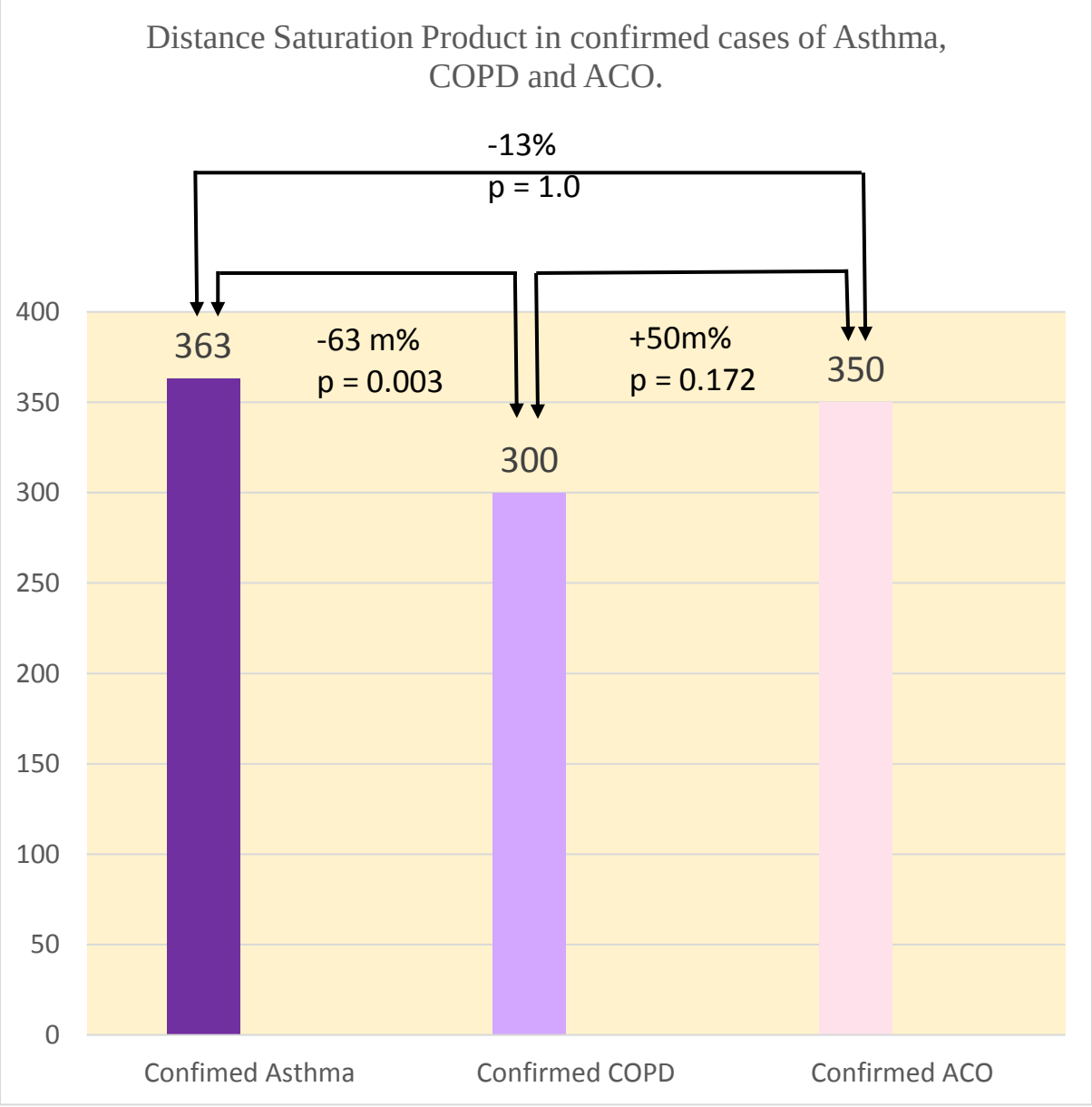


Figure 48 DSP% comparison in confirmed cases of Asthma, COPD and ACO. N = 877

IgE immunoglobulin comparison in confirmed cases of Asthma, COPD and ACO.

Comparing confirmed Asthma with ACO and COPD, the former has a statistically significant, elevation in IgE when compared to the other two. There was no statistical significant difference between confirmed ACO and COPD.

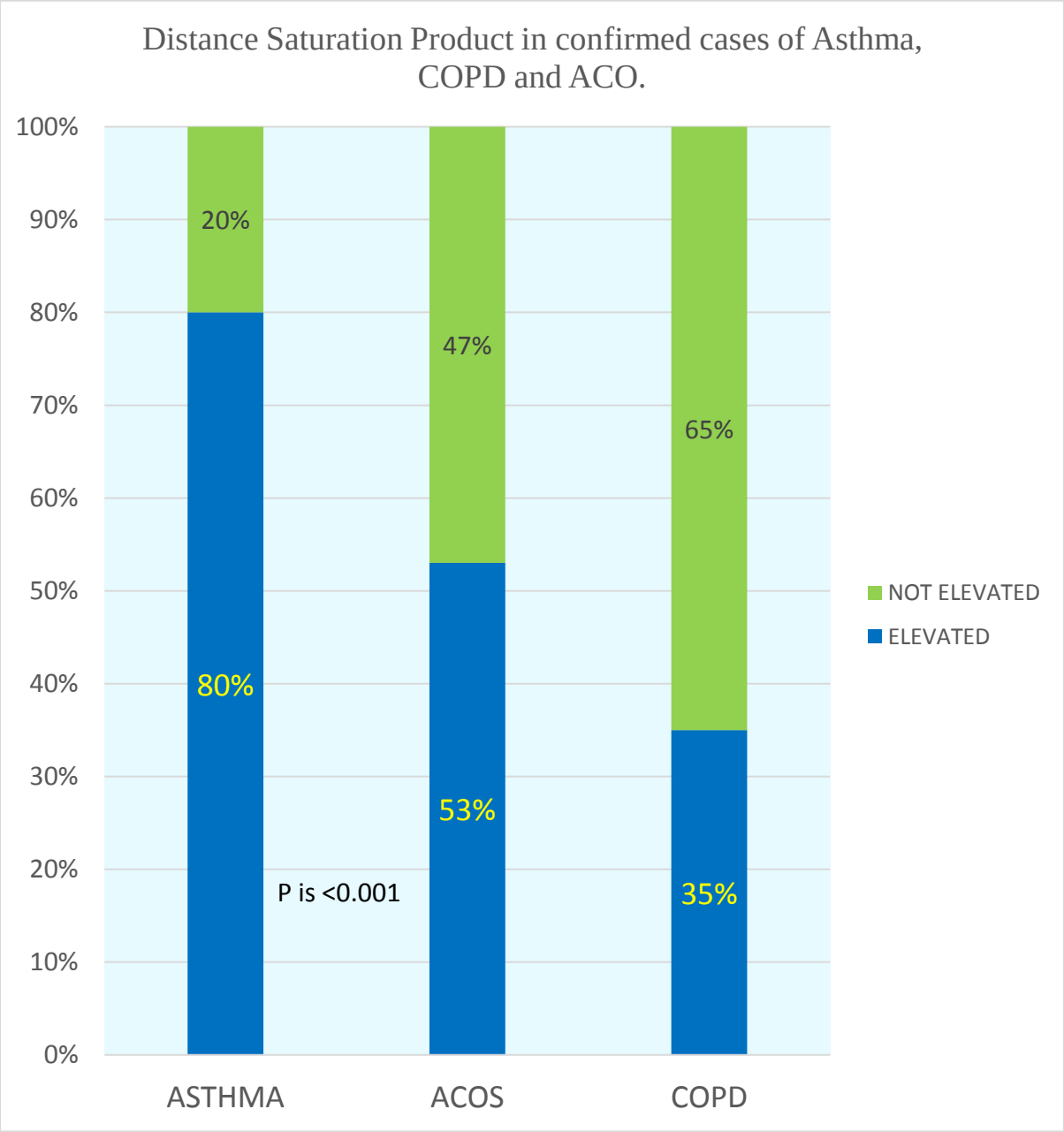


Figure 49 Distance Saturation Product in confirmed cases of Asthma, COPD and ACO. N =877

Peripheral Eosinophilia comparison in confirmed cases of Asthma, COPD and ACO.

Significant peripheral blood eosinophilia is associated with high medical care resource use in Asthmatics. Sputum eosinophilia is more important in identifying eosinophilic asthma.

Peripheral blood eosinophils were found to be elevated in confirmed Asthma and ACO when compared with COPD. But there was no difference between Asthma and ACO.

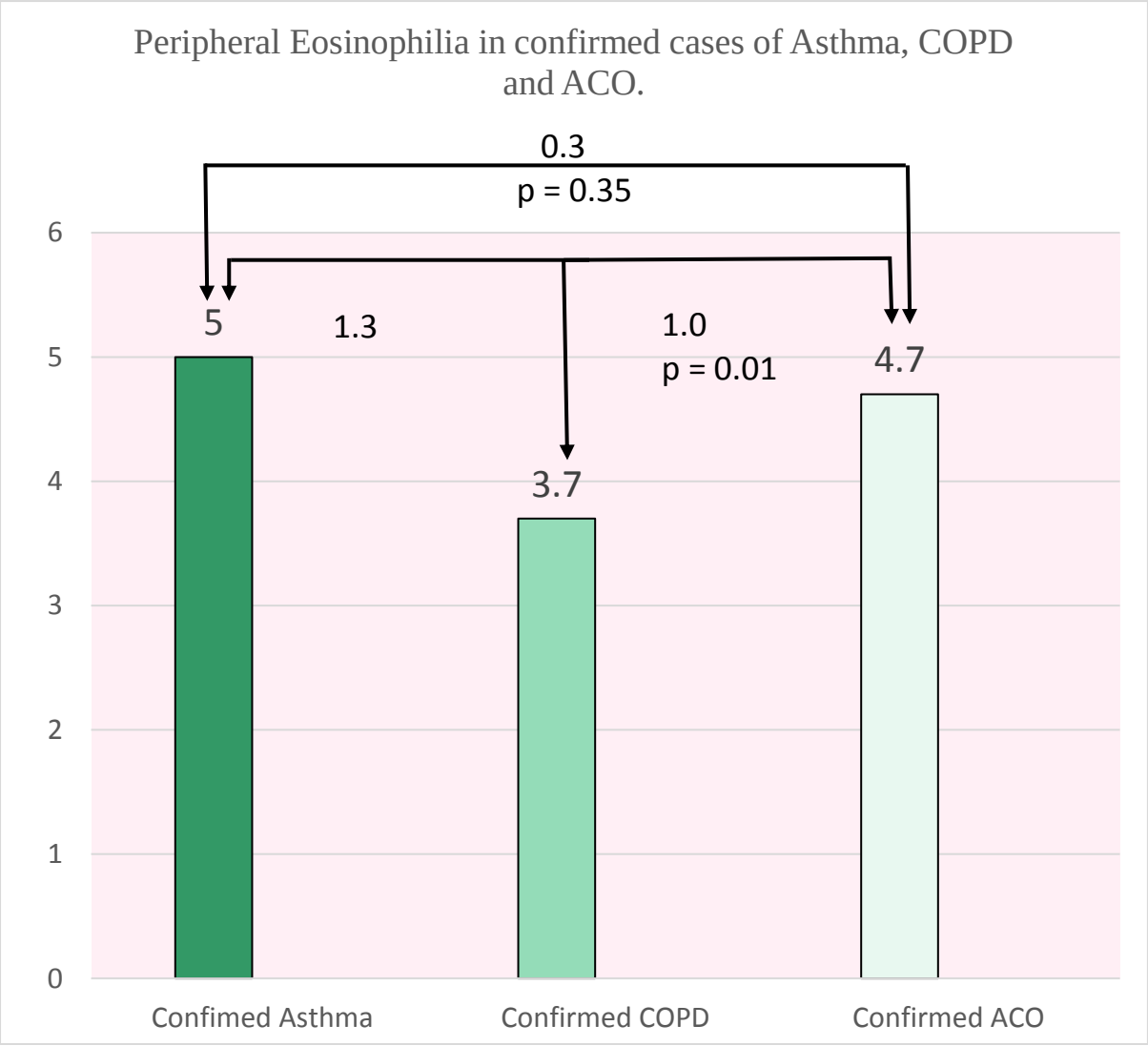


Figure 50 Peripheral Eosinophilia in confirmed cases of Asthma, COPD and ACO. N = 877.

Infective exacerbations in confirmed Asthma, COPD and ACO.

Exacerbations of underlying disease signify poor disease control and will cause rapid deterioration of lung function. Confirmed COPD had worse exacerbation rate compared to asthma or ACO. Per 100 patients in a year, Confirmed COPD patients had 77 exacerbations; Confirmed ACO patients had 4 exacerbations and Asthma patients had 14 exacerbations. Exacerbation of symptoms were more common in COPD 52.8% compared to ACO 41.66% and Asthma 10%. The frequency of exacerbation per patient is also more with confirmed COPD compared to Asthma and ACO.

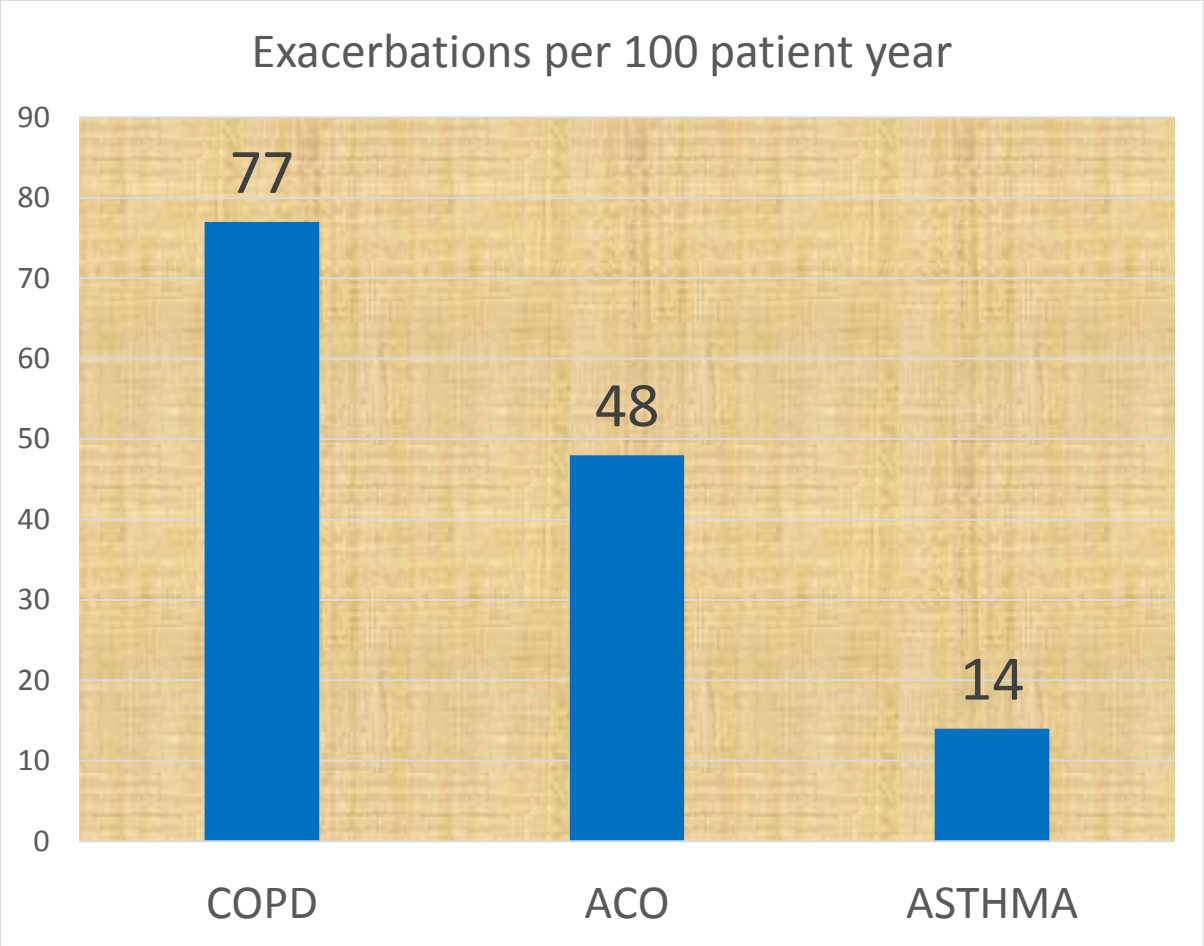


Figure 51 Comparison of exacerbations per 100 patient year

ICU admissions in lifetime

COPD patients generally require more intensive monitoring when they have an exacerbation due to their propensity to develop respiratory failure. 16% Confirmed COPD patients had ICU admissions, compared to the 6% ACO and the 2% Asthma patients.

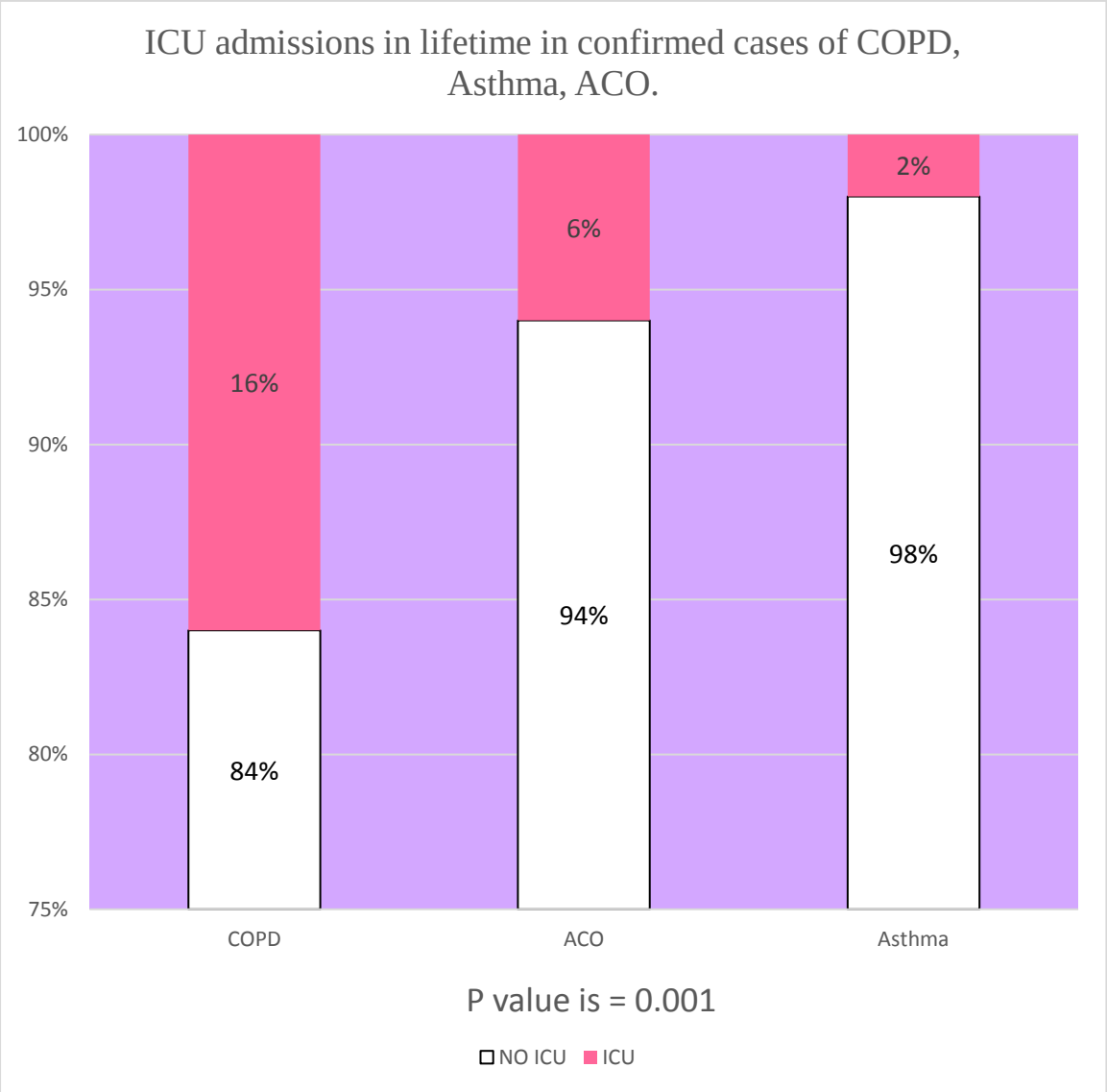


Figure 52 Comparison of ICU admissions in lifetime. N COPD: 104, N ACO: 48 Asthma: 725

NIV and Ventilator need

COPD (17%) patients generally had more need for mechanical ventilation and NIV when compared to Asthma (1%) or ACO (11%).

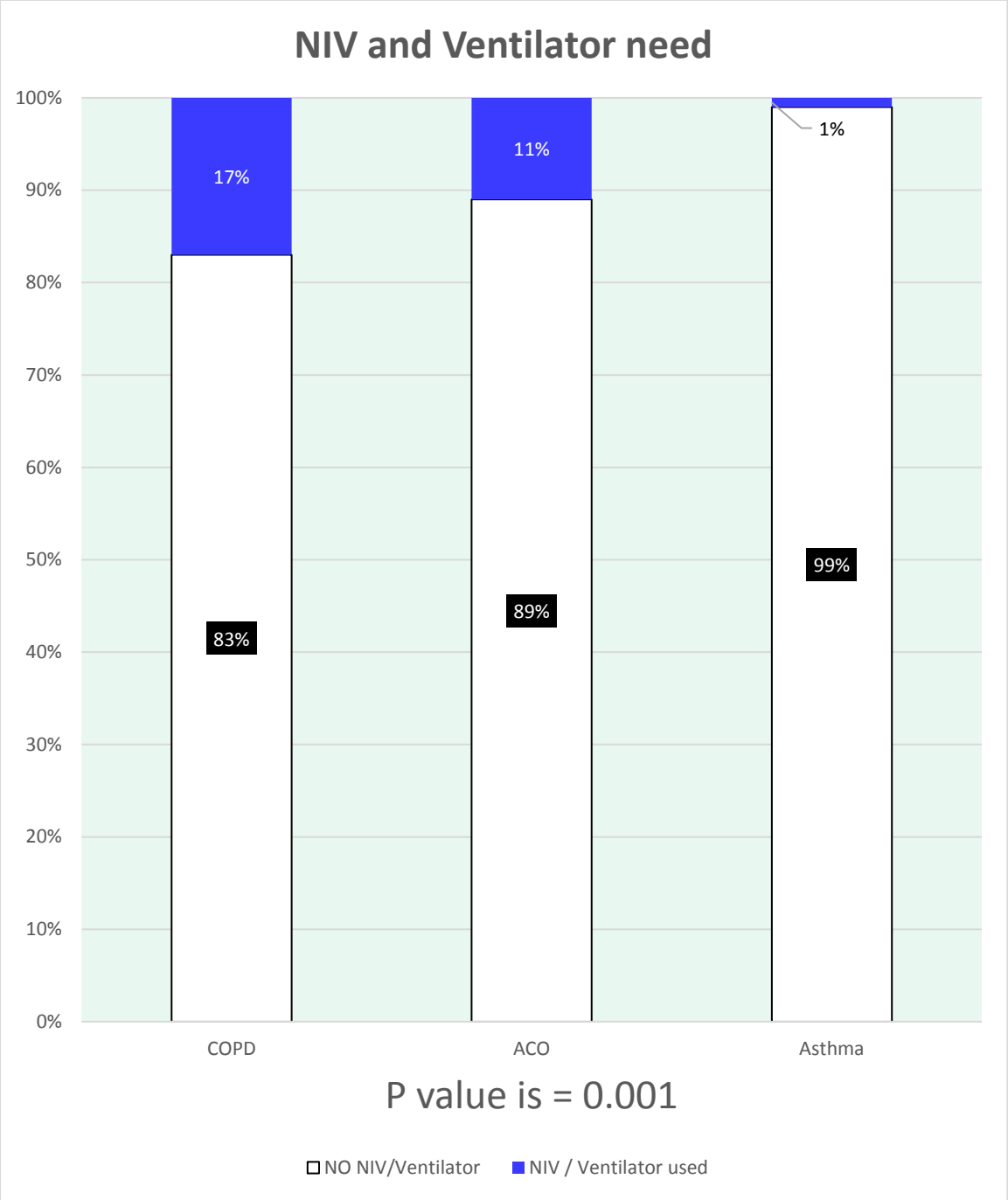


Figure 53 NIV and Ventilator need: COPD: 104, N ACO: 48 Asthma: 725.

Treatment pattern Comparison

6 Asthma patients were inappropriately on anticholinergics only. And 6 COPD patients were on only inhaled corticosteroids. All ACO patients were at least on Inhaled corticosteroids.

Table 6: Treatment pattern in True Asthma, COPD and ACO.

TREATMENT REGIMEN	**FINAL DIAGNOSIS**			**TOTAL**
	BA	COPD	ACO	
SABA ONLY	1	1	0	2
TIOTROPIUM ONLY	6	0	0	6
ICS LABA	261	14	9	284
ICS + SABA	50	1	0	51
MONTELUKAST ONLY	2	0	0	2
ICS LABA MONTEL	197	0	1	198
ICS MONTEL	3	0	0	3
ICS LABA TIOTROPIUM	103	88	38	229
TOTAL	725	104	48	877

DISCUSSION:

ACO is an umbrella term that covers, a set of patients, who have both features of asthma as well as COPD. The degree of dominant symptoms manifestation of one disease over another can be different, yet coexistence of both is what is known as ACO. This includes a wide spectrum of patients that exist in between pure COPD and pure asthma.

There are a lot of criteria for diagnosing ACO ever since 2008. Most of them are simple and includes a previous diagnosis of COPD and spirometry evaluation (76). By some of the earlier criteria the prevalence of ACO was over reported. Over the years there have been multiple studies with different criteria which was discussed earlier. (see page number). Jo YS et al., compared the prevalence rate obtained from different criteria from the same population. The prevalence varied from 31% by using modified Spanish Criteria to 48% using the Platino criteria (28). Due to the lack of consensus across the various groups of respiratory scholars, in 2016 the GINA and GOLD together published a consensus document, proposing a syndromic approach tool to ease and standardize the diagnosis of ACO (1,2). GINA-GOLD guidelines are widely accepted, hence we decided to use this tool to assess the magnitude of ACO in our study.

Miravitlles et al., reported 6.5% of ACO prevalence among COPD patients (31). Golpe et al., reported a prevalence of 5% in smoking COPD and 21% among biomass fuel COPD (30). There are other studied which quote the prevalence of ACO from a previous diagnosis of COPD to be between 11.3% to 18.60% (27,77). Likewise

from a previous diagnosis of Asthma the prevalence of ACO is around 30% (27,29). In our study, the prevalence data for ACO among COPD patients was similar to most studies done in multinational centers, 17%. While there are only few studies done to assess the prevalence of ACO in Asthma patients, the prevalence rate in our study was 2.8%, lower from, than that of COPD as expected.

ACO was generally found to be gender nonspecific. In a study done in the US, Vac Fragoso et. al, found that 67% of their ACO patients were females (23). In another study done by Maria Montes et. Al 65% of the ACO patients were male (77). Jung et al., reported 95% males with ACO (25). In our study 58% of the confirmed ACO were males. The prevalence of ACO was found to be more in males (N = 28) compared to females (N = 20).

Generally the studies have shown that the mean age of diagnosis of ACO was much earlier than COPD (23). There was not much difference in our study. The number of COPD and ACOS patients in the 60+ age group was almost double the number in the 40 – 60 age group. The mean age of patients in each of the groups is as follows: Asthma 46 ± 15, COPD 64 ± 9 and ACOS 62 ± 11.

Similar studied has shown that the prevalence of smoking among diagnosed ACO patients was less than that of COPD. The same trend was seen in our study. However, the prevalence of biomass fuel exposure was higher in ACO in our study compared to Asthma or COPD. Golpe et al, have earlier reported that the prevalence of ACO was more among those who were exposed to BMF.

Family history of asthma in the immediate family member had been consistently shown to be a risk factor for asthma development in various literature. A comparison was done between ten studies by Burke W et. al., sensitivity of the positive family history to predict development of asthma was between 4% to 43%, the positive predictive value was between 11% to 37%, and the negative predictive value was high and between 86% to 97%. Positive family history increases the probability to develop asthma (78). In our study 29% of Asthma and 25% of ACO had a positive family history of Asthma.

Asthmatics can have a normal spirometry at the time of diagnosis, but presence of an obstruction is essential for the diagnosis of COPD and ACO. The GINA syndromic approach fails in this aspect that patients who were diagnosed to have COPD using this tool, 5.7% of them had no obstruction in spirometry. 35.42% of the patients diagnosed as ACO also had no obstruction. However, this could be explained by the fact that the GINA tool provides much weightage to the clinical nature of the illness compared to the actual spirometry values. Similarly, reversibility of obstruction in a previous known COPD patient would be classified as ACO in most criteria. 16% of COPD patients and 31% of ACOS patients have shown reversibility. Of which the 400ml & 12% reversibility, that is almost diagnostic of asthma was also present in 6 COPD and 2 ACOS patients. This again could be explained by the presence of overlap symptoms.

Based on the 6-minute walk test, the exertional desaturation was more common in COPD 33% followed by ACO 12%. Only 6% of asthmatics had significant desaturation. > 4% desaturation was considered significant desaturation in a COPD patient (74,75). Distance saturation product in COPD is known to be lower corresponding to the drop-in saturation with exertion. DSP is more decreased in COPD compared to Asthma or ACO.

IgE elevation is a nonspecific marker of an underlying allergic reaction. Elevated serum immunoglobulin E(IgE) can also be seen in certain infections (parasites) and immune conditions (79).

Significant peripheral blood eosinophilia is associated with high medical care resource use in Asthmatics. Sputum eosinophilia is more important in identifying eosinophilic asthma. Peripheral blood eosinophils were found to be elevated in Asthma and ACO when compared with COPD. But there was no difference between Asthma and ACO

Overall there are a lot of population based studies, disease characterization research, criteria development, morbidity related data, health expenses etc. which are published in increasing numbers over the past few years. Most of the studies have conveyed the idea that ACO have worse outcomes than either Asthma alone or COPD alone. They were found to have worse disease control, worse rates of exacerbations and admission, with increased financial demand on the patient (23,26,77,80).

However, COPD had worse exacerbation rates, poor disease control, more number of admissions and need for ICU and ventilatory care compared to ACO. ACO

was definitely more severe than Asthma in all of the above domains. This finding was seen in a similar study done by Park et al., where pure COPD had worse outcomes than ACO (81).

This could be explained by the fact that in our institution, more than 85% of the ACO patients who were eventually diagnosed, were already on maximal possible treatment with SABA prn, ICS LABA combination, Anticholinergics and oral theophylline. And all of there were at least on Inhaled corticosteroids. ACO closely resembles asthma with fixed airway obstruction which would warrant such a treatment. So are COPD patients with severe obstruction.

Most studies have shown worse exacerbation rate with ACO (77). In our study ACO had worst disease control, but COPD had the most exacerbations per 100 patient years. Also COPD had more ICU admissions and NIV / intubations.

Overall using GINA syndromic approach to diagnose ACO was fairly simple and less time consuming. Not only it helps us to diagnose ACO, it helps us to differentiate bronchial asthma from COPD with ease. This study was an eye opener as to how many of our COPD patients were actually Asthma patients, who were misdiagnosed and over treated.

The GINA tool relies a lot on the clinical features of the disease process. Weightage is given to spirometry in only one of the eleven points. The drawback is that patients who are poor historians can provide incorrect details. This could explain how patients with 400ml reversibility were labeled as COPD. There were a few such patients in our study who were diagnosed as COPD despite having very significant

reversibility, which should definitely be Asthma. A significant percentage of the COPD patients had normal FEV1/FVC ratio. We know that a normal ratio is not compatible with the diagnosis of COPD, but the clinical behavior of the disease would have been very much like COPD.

Hence a few modifications could be made to the GINA-GOLD syndromic approach table tool to avoid such confusions in clinical practice.

LIMITATIONS:

The following are a few of the limitations to the study,

1) The study was a single visit study, in a single center. Follow-up of such patients regularly to see if the same GINA-GOLD tool consistently gives the same diagnosis at each review visit, would strengthen the relevance of the tool.
2) This was a single center study done in India. A multicenter study from across the country would give a better picture of the true state of the disease in our country.
3) Our center is a tertiary care center. Usually difficult to manage obstructive airway disease patients are referred and are managed here. So, this study prevalence rates may not be applicable to the general population and other smaller hospitals.

RECOMMENDATIONS AND FUTURE DIRECTIONS:

The following are a few initiatives/research ideas that could be done in the future:

1) All Obstructive airway disease patients should be subjected to the GINA tool to verify the diagnosis after 6 months of treatment.
2) The efficiency of diagnosing ACO should be compared across the different criteria that are in existence right now and to see how each criteria fare against each other.
3) Treatment response studies on ACO patients for different drugs should be done.
4) Can ACO progress into a COPD? Can ACO be always ACO or the nature of such a diagnosis will change with treatment or time?

CONCLUSIONS:

The primary objectives of the study were achieved. The prevalence of ACO was established in the study population; 17.2% from COPD and 2.8% from Asthma. Overall it was 5.4% of all obstructive airway diseases, obtained from our study population.

This study provides an insight into the prevalence rate in India. ACO per se did not have worse disease control, exacerbation rate, admissions, NIV requirement or exercise desaturation compared to COPD. ACO is worse than Asthma in all the above aspects.

This GINA tool apart from being a tool to identify ACO have also helped us to differentiate COPD from very severe Asthma with fixed airway, which is otherwise very difficult and confusing. Further research is needed to refine the diagnostic criteria, which is the need of the hour.

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Appendix

IRB acceptance letter

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 20, 2016

Dr. Jefferson Daniel J,
PG Registrar,
Department of Pulmonary Medicine,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
The magnitude of Asthma COPD Overlap Syndrome (ACOS) among patients diagnosed as Asthma and COPD.
Dr. Jefferson Daniel J (Employment Number: 29462), PG Registrar Pulmonary Medicine, Dr. D J Christopher,(Employment Number: 14193), Pulmonary Medicine, Dr. Balamugesh T, (Employment Number: 31292), Pulmonary Medicine, Dr. Richa Gupta (Employment Number: 31330), Pulmonary Medicine,

Ref: IRB Min No: 9844 [OBSERVE] dated 07.01.2016

Dear Dr. Jefferson Daniel J,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "The magnitude of Asthma COPD Overlap Syndrome (ACOS) among patients diagnosed as Asthma and COPD" on January 07th 2016.

The Committee reviewed the following documents

1. IRB Application format
2. Proforma
3. Patient Information Sheet and Informed Consent Form (English , Tamil, Malayalam, Hindi)
4. Cvs of Drs. Jefferson Daniel J, D J Christopher, Balamugesh T, Richa Gupta
5. No. of documents 1- 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on January 07th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. RV. Shaji		Professor, Heamatology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. B. J. Prashantham	MA(Counseling Psychol MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centr Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Simon Pavamani	MBBS, MD	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MD, DNB(Endo), Phd(Endo)	Professor, Endocrinology, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "The magnitude of Asthma COPD Overlap Syndrome (ACOS) among patients diagnosed as Asthma and COPD" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:

A sum of 98,680/- INR (Rupees Ninety eight Thousand Six hundred and eighty only) will be granted for 15 months.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 9844 [OBSERVE] dated 07.01.2016

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Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Information Sheet

CHRISTIAN MEDICAL COLLEGE
DEPARTMENT OF PULMONARY MEDICINE

The magnitude of Asthma COPD overlap syndrome in Asthma and COPD patients

Asthma COPD overlap syndrome is a disease which is similar to Asthma and COPD. Asthma is usually seen in children and young people. COPD is usually seen in older people and generally people with a smoking history. Though both asthma and COPD can have similar complaints like cough and wheezing, asthma usually responds well to inhaled medications unlike COPD. But there is now a new entity called "Asthma COPD overlap syndrome" that resembles both Asthma and COPD. It improves with inhaled medications but not fully enough to be called Asthma. This new disease is under diagnosed in people and a lot of patients who are currently treated for asthma or COPD are actually Asthma COPD overlap patients. We are doing this study so that we can find out how many of our patients are actually Asthma COPD overlap syndrome. By doing this we can give appropriate medications to provide maximum benefits.

If you take part what will you have to do?

If you agree to participate in this study, your base line data will be collected. Your previous x rays and spirometry will be reviewed. We will investigate if your previous diagnosis is right. After which appropriate changes in treatment will be made. No additional procedures or blood tests will be conducted routinely for this study.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you because of taking part in this study.

Will you have to pay anything extra to take part in the study?

You will not incur any extra charges for taking part in this study.

What happens after the study is over?

You may or may not benefit from the study that you are a part of. However the conclusions drawn from this study will be useful to manage similar patients in future.

Will your personal details be kept confidential?

The results of this study may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

About 2500 patients are participating in this study.

Performa

ACOS STUDY

DEPARTMENT OF PULMONARY MEDICINE, CMC VELLORE.

Serial No	Name	Age	Sex	Hospital No	Doctors Diagnosis	Date

1. How long do you have this problem?
2. Total no of hospital admissions:
3. ICU admissions if any:
4. Have you been intubated before/NIV?
5. Assessment of symptom control:

In the past 4 weeks, has the patient had:	Yes	No	Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than 2/week?			None of these	1-2 of these	3-4 of these
Any night awakening due to asthma?					
Reliever needed more than 2/week?					
Any activity limitation due to asthma?					

6. Do you have a family history of Asthma?
7. Do you have allergy and rhinitis?
8. Bio mass fuel exposure? Yes/No. If yes, bio mass fuel index: _____
9. Do you smoke? Yes/No. If yes, How much? In pack years: _____
10. Current treatment regimen:

ICS only	LABA only	SABA only
ICS+LABA	ICS+SABA	LAMA only
ICS+LABA+LAMA	ICS+LAMA	ICS+LABA+SABA

14. Are you on regular follow up y/n? Yes/No (at least 2/yr. for 3 yrs.)
15. How many years of MDI use?
16. Are you regular on MDIs?
17. Effort tolerance before initiating treatment: Distance: MMRC
18. Effort tolerance after initiating treatment (at least 6 months): Distance: MMRC
19. Spirometry:

Date	Spiro 1	PRE BD	%	POST BD	%	D%	
	FVC						
	FEV1						
	FEV1/FVC						
	Spiro 2						
	FVC						
	FEV1						
	FEV1/FVC						

% reversibility: Reversible volume:

	ASTHMA	**COPD**
Age of onset	Before 20	After 40
Pattern of symptoms	1. Variation over minutes, hours or days. 2. Worse during the night or early morning. 3. Triggered by exercise, emotions including laughter, dust or exposure to allergens.	1. Persistent despite treatment. 2. Good and bad days but always daily symptoms and exertional dyspnea 3. Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers.
Lung function	Record of variable airflow limitation.	Record of persistent airflow limitation.
Lung function between symptoms	Normal	Abnormal
Past history / Family History	1. Previous doctor diagnosis of asthma. 2. Family history of asthma and other allergic conditions.	1. Previous Doctor Diagnosis if COPD, Chronic bronchitis or emphysema. 2. Heavy exposure to risk factor: tobacco smoke, bio mass fuel.
Time Course	1. No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year. 2. May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks.	1. Symptoms slowly worsening over time (progressive course over the years). 2. Rapid - acting bronchodilator treatment provides only limited relief.
Chest X ray	Normal	Hyperinflation

20. 6 minute walk test:

- SpO2 baseline: End: Min:
- Distance saturation product (m%):
- Distance walked: Predicted: % predicted:

21. Study Diagnosis:

Consent to take part in the study

The magnitude of Asthma COPD overlap syndrome in Asthma and COPD patients

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Study Number: _____

Subject's Initials: _____

Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).[ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____Signature:

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

_____